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END RESULTS IN THE TREATMENT OF GASTRIC CANCER

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(From the Gastric Service of the Memorial Center)

THE patient who is found to have carcinoma of the stomach has an uncertain future. The prognosis, or future course, of this patient undoubtedly depends upon a host of factors and findings which are either initially or subsequently apparent to the physician. The significance of these factors in regard to the prognosis can only be assumed by study of past experience or end results.

This study of end results includes all patients with adenocarcinoma of the stomach seen by members of the Gastric Service of the Memorial Center in the years 1931 through 1955. Survival for 5 years after treatment without evidence of local recurrence or metastasis is the customary index of clinical cure. Although this may not be invariably reliable, statistics based upon 5-year survival without cancer were used in many phases of this study as an index of curability.

Classification has been based upon the patients' suitability for surgical treatment. The designation "inoperable" was reserved for those patients who, at the time of the initial examination, had distant metastasis or serious medical contraindications for surgical intervention. The smaller number of patients who refused surgery was also included in this category.

All patients submitted to surgery were considered operable. At the time of exploration the operative findings determined subsequent classification of this group. Those operations in which all gross cancer could be removed were considered curative operations. All operations in which gross cancer was left in situ were classified as noncurative operations. Noncurative procedures included exploratory laparotomy without resection, bypass operations, and palliative resection.

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Postoperative mortality in this study refers to death occurring within 30 days of the operation. For statistical study of the effect of other variables on end results, the postoperative mortality was often eliminated.

The 1.9 per cent of patients who failed to return for follow-up examinations within the 5-year period after treatment have been considered dead of cancer. After a 5-year observational period those who failed to return for follow-up or died of causes other than cancer have been considered in terms of 5-year survival figures as free of cancer.

OPERABILITY AND RESECTABILITY

General Considerations.—Of the entire series of 1,623 patients observed in the years 1931 through 1955, 1,315 (81.0 per cent) were submitted to some form of operation. Due to the generally held pessimistic view toward cancer of the stomach in the earlier period (1931 through 1940), only 65.8 per cent were considered worthy of surgical treatment. In contrast to this, 90.8 per cent of patients seen in the years 1951 through 1955 were deemed operable.

Of the entire series, 33.9 per cent of 1,623 patients underwent definitive or curative resections. Changing concepts in the management of these patients were again demonstrated when comparing resectability rates in 2 chronologic periods. In the earlier years (1931 through 1940), resection was rarely performed except with the intent of cure, or in 15.5 per cent of all patients seen. The frequent performance of some form of bypass procedure, such as gastrostomy, jejunostomy, or gastroenterostomy reflected the general attitude of surgeons toward most patients with cancer of the stomach. In the years 1941 through 1955 the simultaneous development of endotracheal anesthesia, thoracic surgery, and the discovery of antibiotics enabled surgeons to offer resection to a larger number of patients (41.6 per cent).

Curative Operations.—Subtotal gastrectomy may be performed for cancers of the antrum or of the cardia and is therefore designated as distal or proximal. Inasmuch as the majority of resectable or curable cancers are localized manifestations of the disease, it is not surprising that subtotal gastrectomy was performed in 71.1 per cent of curative resections as opposed to 28.8 per cent of patients in whom total gastrectomy was carried out. Proximal subtotal gastrectomy, or resection of the gastric cardia, was performed in 20.7 per cent of the group of subtotal operations.

In the group of patients requiring removal of the entire stomach, the extended total gastrectomy was performed in 48.7 per cent of the cases. Though this operation is one of recent development, it has, nevertheless, replaced simple total gastrectomy in our hands whenever complete ablation of this organ is indicated. The reasons for this more radical approach are discussed elsewhere.[3, 5]

Noncurative Operations (Palliative).—Noncurative operations comprised roughly half of the procedures performed throughout the entire period of study. There was a change over the years in the approach to noncurative operations for gastric cancer. Whereas some form of bypassing procedure (gastrostomy, jejunostomy, or gastroenterostomy) comprised 97.7 per cent of all

palliative operations in the years 1931 through 1940; only 25.7 per cent of similar cases were so treated from 1951 through 1955. This means that 74.3 per cent of all palliative operations in the latter period were resections. Subsequent study of our material has revealed that patients with incurable gastric cancer were appreciably benefited only by resectional procedures.[1]

Factors That May Influence Operability and Resectability.—

Sex: Of the 1,623 patients in this series, 1,116 (68.8 per cent) were men, and 507 (31.2 per cent) were women. Resectability in men was 34.1 per cent and in women 33.5 per cent.

Age: Our data demonstrate a progressive improvement in the resectability rates with increase in age from 30 to 80 years (Fig. 1).

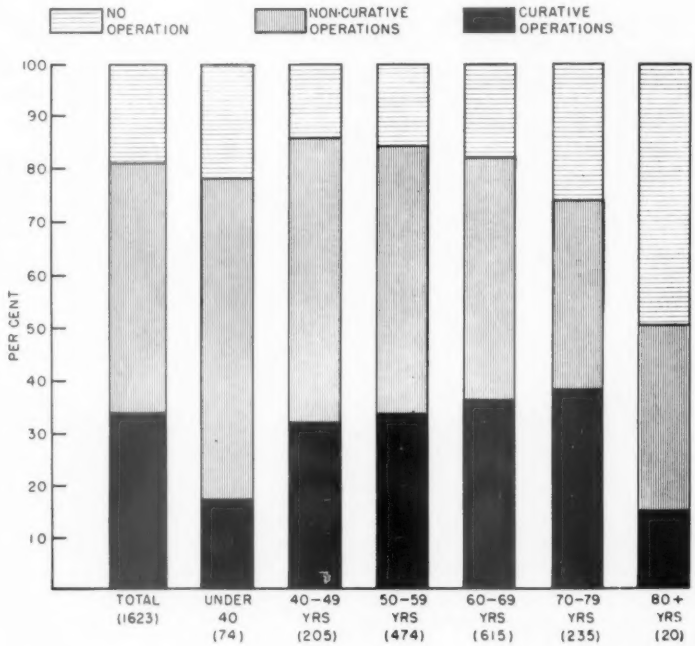

Fig. 1.—Operability and resectability in relation to age of patient.

Duration of symptoms: The clinical histories of 1,608 of the 1,623 patients were adequately documented to study the effect of this factor on operability and resectability. The group with a short history of symptoms was composed of a higher proportion of inoperable patients than the group with a longer history. If the symptoms were less than 3 months in duration, inoperability was 17.6 per cent. This figure fell to 8.6 per cent when symptoms were over 3 years in duration. The effect of the duration of symptoms on resectability was similar but less marked. If the symptoms persisted over 2 years prior to treatment, 40.4 per cent of the cancers were found to be resectable. In patients treated soon after the onset of symptoms (less than 3 months), the resectability rate was only 35.9 per cent.

Early diagnosis has been considered of prime importance in our attempt to improve the results of treatment of many cancers. Despite the inherent logic of establishing diagnosis and instituting treatment early in the course of

the disease, study of our material would seem to demonstrate no significant benefit from early diagnosis (from the standpoint of operability and resectability rates).

To study in more detail the relationship of the duration of symptoms to these figures, the 25-year period was separated into Period I (1931 through 1945) and Period II (1946 through 1955). There were 858 patients observed in Period I and 770 patients in the more recent period. In Period I, 15.8 per cent of the patients had a diagnosis of gastric cancer made prior to 3 months of onset of symptoms, while, in Period II, 24.8 per cent of the patients had symptoms for less than 3 months. It should be noted also that operability improved from 73.3 per cent in Period I (1931 through 1945) to 89.6 per cent in Period II (1946 through 1955). The proportion of curative resections increased from 26.0 per cent in Period I to 42.7 per cent in Period II. Has this improvement in operability and resectability been due to earlier diagnosis or to other factors? In the latter period of this study (1946 through 1955), the proportion of curative resections was definitely higher than in the earlier period, but this was not limited to those who had their diagnosis made early. We found improvement in resectability in all groups without any relationship to duration of symptoms. In regard to improvement in resectability figures in the later years, other factors may be more significant. A combination of a more aggressive attitude and a larger number of surgeons well versed in thoracic as well as abdominal techniques has probably been a more potent factor than earlier diagnosis in the high resectability rates of Period II (1946 through 1955).

Type of symptomatology: It has been observed that the symptoms of carcinoma of the stomach follow 3 general patterns: prolonged "indigestion," the ulcer syndrome, and weakness due to anemia (Table I).

TABLE I. TYPE OF SYMPTOMATOLOGY IN RELATION TO OPERABILITY AND RESECTABILITY AND 5-YEAR SURVIVAL (1941-1950)

TYPE OF TREATMENT	TOTAL CASES		NONSPECIFIC INDIGESTION		ULCER SYNDROME		ANEMIA ONLY	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Distribution as to type of symptomatology:								
Total cases	808*	100.0	669	82.8	88	10.9	51	6.3
Five-year survivors	72*	100.0	46	63.9	18	25.0	8	11.1
Type of symptomatology in relation to operability and resectability:								
Total cases	808*	100.0	669	100.0	88	100.0	51	100.0
Inoperable cases	114	14.1	98	14.6	6	6.8	10	19.6
Noncurative operations	348	43.1	297	44.4	34	38.6	17	33.3
Curative operations	346*	42.8	274	41.0	48	54.5	24	47.0
Five-year survivors	72*		46		18		8	
Percentage based on total cases		8.9		6.9		20.4		15.7
Percentage based on curative operations		20.8		16.8		37.5		33.3

*In 2 instances the type of symptomatology was not indicated.

For this study 808 consecutive cases from the period 1941 through 1950 were classified by the character of their symptomatology. Resectability was highest

in those patients with the ulcer syndrome (54.5 per cent), followed by 47 per cent for those with anemia only, and 41 per cent for the group complaining of nonspecific indigestion. The first 2 symptom types, although in the minority, accompanied what appears to be more favorable lesions from the point of view of resectability.

Presence of abdominal mass: The presence of a palpable abdominal mass if often described as an ill-fated omen in this disease. For evaluation of the importance of this finding, we tabulated the opinions stated in the records of 810 patients seen in the years 1941 through 1950 (Table II). The presence of a mass did not offer as good a chance for curability as the absence of palpable cancer. On the other hand, the fact that 30.7 per cent of this group had a lesion that was readily resectable offers ample evidence that the internist or surgeon should not be discouraged from advising laparotomy when cancer of the stomach is large enough to be readily palpable.

TABLE II. PRESENCE OF ABDOMINAL MASS IN RELATION TO OPERABILITY AND RESECTABILITY AND 5-YEAR SURVIVAL (1941-1950)

TYPE OF TREATMENT	TOTAL CASES		MASS ABSENT		MASS PRESENT	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Total	810	100.0	543	100.0	267	100.0
Inoperable cases	114	14.0	58	10.7	56	21.0
Noncurative operations	348	43.0	219	40.3	129	48.3
Curative operations	348	43.0	266	48.9	82	30.7
Five-year survivals	74		60		14	
Percentage based on total cases		9.1		11.0		5.2
Percentage based on curative operations		21.3		22.6		17.1
Distribution as to mass	810	100.0	543	67.0	267	33.0

POSTOPERATIVE MORTALITY

The 1,315 patients surgically treated during the 25 years from 1931 through 1955 were used for determination of postoperative mortality statistics. Of the entire series there were 197 patients (15 per cent) who died in the hospital as a direct result of surgery. Over the years there appeared to be very little change in this figure.

Postoperative Mortality Following Curative Operations.—In general the over-all mortality after curative operations (18.0 per cent) was slightly higher than for noncurative procedures (13.2 per cent), but the inclusion of a large number of patients treated by total and extended total gastrectomy in the former group may help explain this finding. As greater familiarity with surgery of the stomach was gained, hospital mortality for subtotal gastrectomy for the cure of cancer declined to 6.1 per cent in the past 5 years (1951 through 1955). In the years 1946 through 1950 the operative mortality for curative total gastrectomy was only 5.7 per cent. Decrease in the death rate after proximal subtotal gastrectomy was slow but definite when cure was possible (11.1 per cent in the 1951 through 1955 period).

The postoperative mortality for all forms of total gastrectomy in this series was 23.3 per cent. The more frequent use of extended total gastrectomy over simple total removal of the stomach has brought additional risks to the patient. Twenty-three per cent of 61 patients so treated from 1951 through 1955 succumbed following surgery.[3]

Postoperative Mortality Following Noncurative Operations.—The goal of palliation should be relief of symptoms for the longest period of time possible.[1] Subtotal gastrectomy, which comes closest to this ideal, and bypassing operations (such as gastrostomy and gastroenterostomy) were accompanied by similar hospital mortality rates (17.9 and 16.8 per cent). In more recent years (1951 through 1955), death after bypassing procedures (26.9 per cent) has about equaled that of total gastrectomy when employed in the incurable case. It must be emphasized that a high operative mortality was associated with all operations on the incurable patient.

The postoperative mortality following noncurative total gastrectomy was 27.7 per cent. From the point of view of operative mortality alone, with only an occasional exception, total gastrectomy should not be carried out as a noncurative procedure. The surgeon must not commit himself to such extensive operations until he is quite sure of removing all gross signs of cancer. If the indications exist for palliative resection of the entire stomach, the extended technique is contraindicated. The simpler resection techniques are therefore preferred when palliation is the goal.

Factors Influencing Postoperative Mortality Following Curative Resections.—

Age: All patients under the age of 40 in our series survived surgery. With each succeeding decade postoperative mortality increased from 6.0 per cent of those in the 40- through 49-year-old group to 23.6 per cent of those undergoing gastrectomy after the age of 70. Many elderly patients are poor operative risks, and yet a way must be found to remove the gastric cancer despite infirmity.

Postoperative mortality after total gastrectomy was higher than after subtotal gastrectomy, increasing with each decade of life. Mortality following extended total gastrectomy in patients over 70 years of age was unduly high in our series.[3] In the elderly patient the possible advantages of increased opportunity for cure by such radical surgery seemed to be outweighed by the postoperative mortality.

Size of tumor: The size of tumor would seem to bear a direct relationship to postoperative mortality after gastrectomy. The cases were subdivided as to size of tumor and the postoperative mortality determined for each group.

The lowest postoperative mortality (7.8 per cent) occurred in the small group of cases where the tumor proved to be less than 4 cm. in diameter. On the other hand, 27.5 per cent died as a result of surgery when the tumor was over 9 cm. in diameter. The technical factors associated with the removal of smaller tumors were not as difficult to solve as in those cases where a similar

operation was utilized but the cancerous process was large. The larger tumors also frequently forced the surgeon to perform multiple organ resections and thereby tended to increase postoperative mortality.

FIVE-YEAR SURVIVAL

Methods of Reporting End Results.—For the purpose of this discussion the statistics were concerned solely with adenocarcinoma of the stomach. We included all patients seen on the Gastric Service of the Memorial Center, New York, from 1931 through 1950, for the 5-year survival study.

It was useful for certain comparisons to calculate statistics on the basis of those patients whose lesions were amenable to curative resection. On this basis 21.6 per cent (91) of all patients subjected to curative resections (422) remained well for 5 or more years (Fig. 2). This successful group represented only 7.1 per cent of the total experience. In evaluating the treatment of patients with cancer, it has been observed that a significant number succumbed to the disease after the 5-year period generally accepted as that of clinical or definitive cure. This has been especially true of the course of such diseases as malignant melanoma, lymphoma, mammary cancer, and synovial sarcoma. In our series of 5-year survivals after curative treatment of gastric cancer, there were 11 patients not classified as 5-year "cures," inasmuch as to our knowledge they died of cancer subsequent to the end of the 5-year period. Our estimates of the clinical cure of gastric cancer treated at the Memorial Center are therefore designated as absolute rather than definitive.

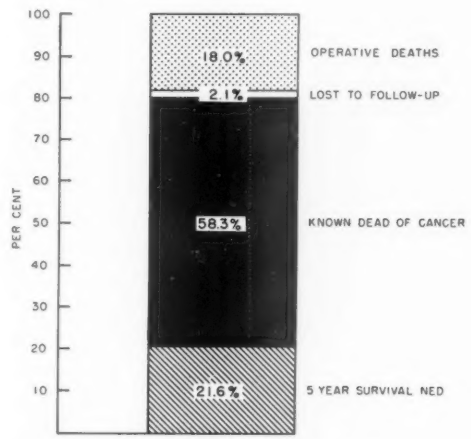

Fig. 2.—Results of curative resections.

To evaluate the importance of clinical and pathologic variables in regard to survival after treatment, it was found useful and more meaningful to exclude postoperative mortality from our calculations. This eliminated the effect these same factors had on postoperative mortality as well as resectability. The 91 patients who lived 5 years without recurrence repesented 27.0 per cent of the 337 patients surviving curative resection (1931 through 1950). Perusal of Fig. 3 will demonstrate quite clearly these various methods of reporting end results.

Improvement in End Results.—The over-all survival statistics quoted above concern the 20-year period from 1931 through 1950. In the first half of this period only 3.6 per cent of "total experience" remained free of cancer 5 or more years following treatment. In the second 10 years (1941 through 1950) the cure rate increased to 9.1 per cent. The last 5 years of this period (1946 through 1950) were accompanied by a 5-year salvage of 11 per cent. This increase in 5-year survival over the period of study was paralleled by an increase in surgical aggressiveness.

Clinical Features Affecting 5-Year Survival.—

Sex: The 5-year survival rate for men was 28.3 per cent, and for women this figure was 24.0 per cent.

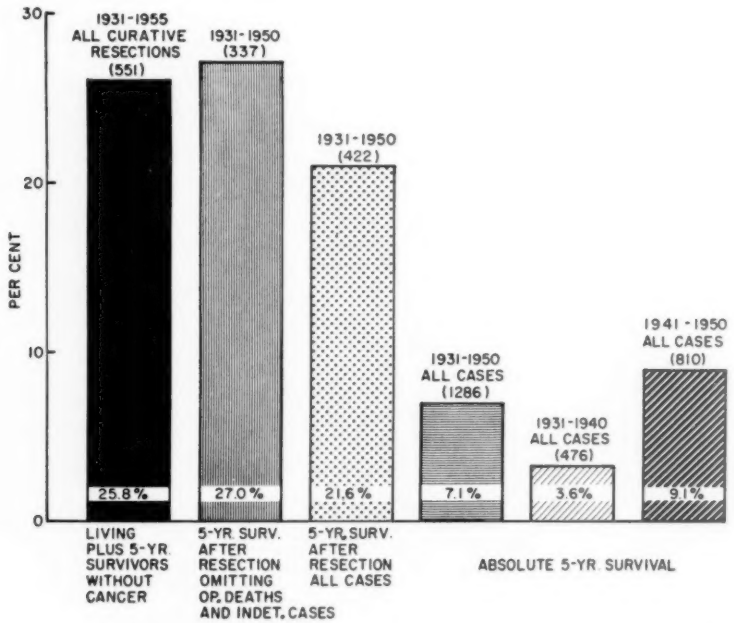

Fig. 3.—Comparison of methods of reporting end results.

Age: It was apparent that resectability was affected adversely by the youth of the patient. When the 5-year results of curative resection, excluding postoperative deaths, were related to age, similar conclusions were apparent. Inasmuch as we have demonstrated a definite increase in curability in the elderly patient, it is obvious that any gain in lowering the postoperative mortality for those older patients could significantly improve our over-all results (Fig. 4).

Duration of symptoms: Of the total number of 422 patients subjected to resection for cure, there were data on duration of symptoms in 419 instances (Fig. 5). Those patients who received treatment during the first 3 months of symptoms were less likely to remain well (15.3 per cent) than those undergoing gastric resection after 6 to 24 months (26.1 per cent). Further evidence that delay in diagnosis was not always unfavorable was shown by the number (15)

reprieved after a duration of symptoms lasting 2 to 3 years prior to surgery. Even more remarkable, there were 11 operations resulting in clinical cure after a symptomatic warning of 3 to 5 years (Fig. 5).

The diagnosis of gastric cancer had been established within the first 3 months of the initial symptoms in 24.8 per cent of cases during the past decade.

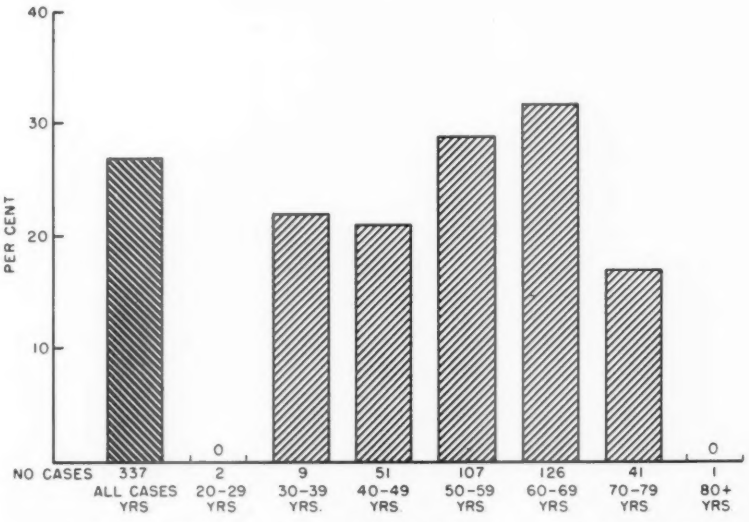

Fig. 4.—Five-year survival in relation to age of patient.

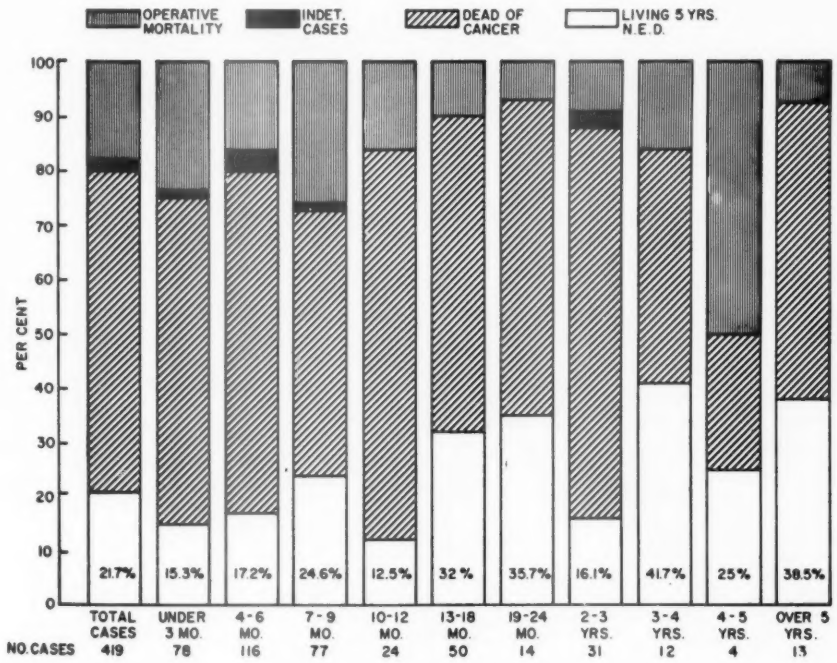

Fig. 5.—Five-year survival in relation to duration of symptoms.

This figure for the period 1931 through 1945 was 15.8 per cent. This factor has not been responsible for the increase in cure rate of this disease, if we consider the 5-year results in terms of duration of symptoms. The resectability

rate increased in the second period, as described previously, but this was also unrelated to early diagnosis. This seems to indicate that a far more fulminant variety of gastric cancer was usually encountered in the patient who sought diagnosis within 3 months of the first symptom. Even the most radical resection of these aggressive varieties of cancer usually did not effect a favorable outcome.

In spite of delay, cure of the disease may be obtained by adequate surgical correction in a large number of instances. To improve results, education of the public and physicians must be re-emphasized in the direction of the realization that any persisting variety of indigestion or alteration from normal gastrointestinal comfort is worthy of medical consultation and radiologic study. If there were recognition of the fact that unobtrusive alteration in digestion may be attributed to cancer of the stomach and if all ulcers of the stomach were viewed with the same suspicion as a lump in the breast, a "short" history might be of favorable, instead of almost fatal, significance.

Type of symptoms: The patients in our series were classified according to type of symptomatology, as outlined in the discussion of factors affecting operability and resectability. The patients with the usual type of nonspecific gastric symptoms comprised 82.8 per cent of all patients, and this group was found to have only a 6.9 per cent opportunity for 5-year survival. On the other hand, 20.4 per cent of those patients with typical ulcer syndrome and 15.7 per cent of patients suffering from anemia only were clinically cured of gastric cancer (Table I). These differences were even more marked if resection survivors were the basis for calculating 5-year "cures." Although the latter 2 groups were small, it would appear from these data that the type of symptomatology is a very important prognostic feature in patients with gastric cancer.

Presence of a palpable abdominal mass: This preoperative finding was associated with a diminished resectability, as described, but this was by no means low enough to discourage exploratory laparotomy. It can be seen in Table II that patients with a palpable mass, when the cancer was resectable, had nearly as great an opportunity for cure as the mass-negative group (17.1 per cent as compared to 22.6 per cent). Although resectability and curability were lower when an epigastric mass was palpable, the prognosis was by no means hopeless and the usual measures directed toward the cure of the patient seem amply justified.

Pathologic Features Affecting 5-Year Survival.—

Location of tumor in the stomach: For descriptive purposes the stomach was divided into 3 surgical sections: proximal (cardia), middle (pars media), and distal (pyloric antrum). When more than one segment of the stomach was involved by cancer the lesion was described as extensive. Excluding postoperative mortality, the 5-year survival rate following curative resection was 33.5 per cent for carcinoma of the pars media, 29.8 for carcinoma of the distal segment, 19.0 for carcinoma of the proximal segment, and 13.6 for extensive cancers.

The outlook for the patient with carcinoma of the middle segment was, therefore, nearly twice as optimistic as for the patient with carcinoma located in the cardia. Although neoplasms of the pars media metastasize freely in all

directions, more generous resection and wide lymph node removal may well have been responsible for the higher cure rate. The tendency for carcinoma of the cardia to extend proximally into the esophagus and to nodes in the mediastinum probably renders cure much more difficult to attain. With cancer of the distal segment, the close proximity of the pancreatic head, mesenteric vessels, and the hepatic triad renders dangerous, and even impossible, any realistic wide dissection inferiorly or on horizontal planes. The relatively high survival rate for cancer of the antrum (29.8 per cent) was probably due to the higher frequency of the ulcerocancers in this region.

Size of tumor: In the analysis of postoperative mortality, it was found that there was a direct relationship to the size of the tumor; that is, the greater the extent of the primary process, the higher the operative mortality. For the purpose of this particular aspect of study, the size of the tumor was related to the curative results. When the carcinoma was under 4 cm. in diameter, 27.6 per cent of the operative survivors remained clinically cured. Only 19.5 per cent of patients harboring gastric cancers over 9 cm. in diameter remained well over 5 years without recurrence.

Gross type of tumor (Borrmann classification): The gross pathologic characteristics of the tumor removed by curative resection were carefully studied to determine if there were features affecting prognosis. All material was subjected to Borrmann's criteria. By far the highest proportion of the surgical material (150 of 337 cases, or 44.5 per cent) was described as "ulcerating and infiltrating," or Borrmann Group III. This gross type represents the "common garden variety" of gastric cancer. The remaining lesions were almost evenly divided among polypoid (I), ulcerating (II), and infiltrating (IV) gross types. By a study of operative survivors only, the gross type of tumor was related to 5-year survival. The cure rate following resection was 44.8 per cent of the polypoid tumors (I) and 45.5 per cent for ulcerocancer (II). Of the 91 patients that were clinically cured of their cancer, 61.6 per cent had Borrmann I or Borrmann II lesions. The Borrmann III tumors were the most common type and in contrast to the noninfiltrating lesions, only 20.7 per cent of the Type III operative survivors were alive without cancer after 5 years. The most malignant variety of gastric cancer was Borrmann IV and only 4 patients with this extensive infiltrating lesion (6.3 per cent) remained well for the 5-year period.

Invasion of serosa: Of the 337 survivors of curative resection, penetration of the gastric serosa by cancer occurred in 182 (54 per cent). Only 20.8 per cent of these patients remained free of cancer for 5 years, as compared to 34.1 per cent of those patients in whom the cancer had remained in the mucosal and muscular layers.

Microscopic grade of tumor: Despite some variation within individual lesions, the tumors were graded from their microscopic appearance. Broders' classification was used, with Grade I to IV in the order of increasing anaplasia. Grade I lesions were uncommon (4.7 per cent) and Grade II was assigned to one-third of the tumors (33.4 per cent). There was a preponderance of Grade III and IV tumors, and together they represented 61.9 per cent of the 337

TABLE III. FIVE-YEAR SURVIVAL IN RELATION TO METASTASIS TO LYMPH NODES (1931-1950)

TYPE OF RESECTION AND RESULT	ALL SURVIVORS		NODES NEGATIVE		NODES POSITIVE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
All survivors	91	100.0	62	68.1	29	31.9
A. Subtotal gastrectomy	81	100.0	55	67.9	26	32.1
1. Distal Segment	69	100.0	47	68.1	22	31.9
Living on Dec. 31, 1955	55	100.0	41	74.5	14	25.5
Lost to follow-up 5 years without cancer	3		2		1	
Died of other causes 5 years without cancer	11		4		7	
2. Proximal segment	12	100.0	8	66.7	4	33.3
Living on Dec. 31, 1955	10		7		3	
Lost to follow-up 5 years without cancer	2		1		1	
B. Total gastrectomy	8	100.0	5	62.5	3	37.5
Living on Dec. 31, 1955						
C. Extended total gastrectomy	2	100.0	2	100.0	0	0.0
Living on Dec. 31, 1955						

specimens evaluated. In the small group (15) of Grade I cancers, 10 of the patients lived 5 years without recurrence. Of the patients with Grade II tumors, 41.5 per cent were clinical cures. As we ascended the scale in regard to microscopic grade, the chance of cure became proportionally smaller (23.9 per cent for Grade III and 12.7 per cent for Grade IV).

METASTASIS TO LYMPH NODES

General Consideration.—The presence or absence of metastasis to the lymph nodes in the perigastric tissues is well recognized as the most important single prognostic feature, once the lesion has been successfully and radically removed. The more extensive the resection and the more carefully the extragastric tissues are studied, the more numerous will be the lymph nodes available for study. This has been beautifully demonstrated by Sunderland and associates.[8] Using a clearing technique, they found an average of 35 nodes in each surgical specimen, many times more than were recovered in a routine study of specimens after subtotal gastrectomy.

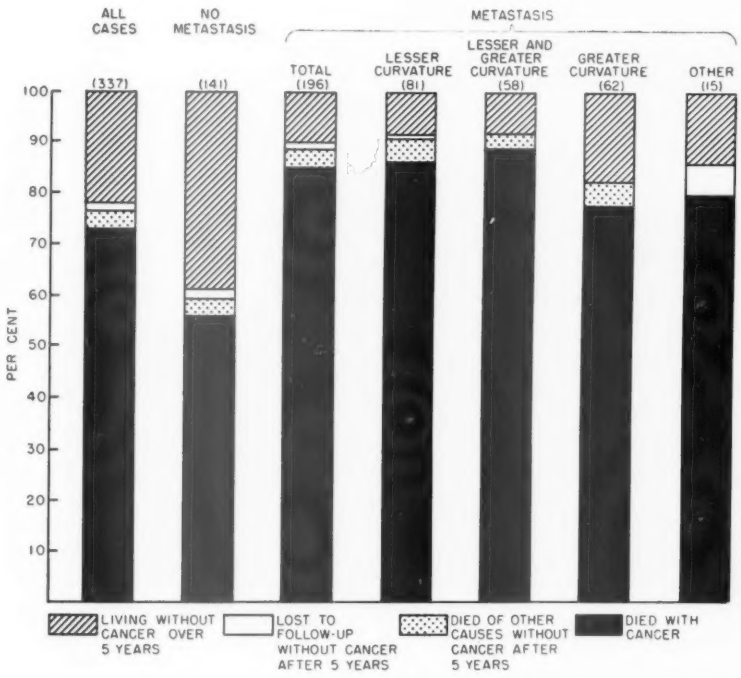

Fig. 6.—Five-year survival in relation to lymph node metastasis.

From 1931 through 1950, there were 91 patients who survived resection for at least 5 years without local recurrence or metastasis. In 62 (68 per cent) nodal metastasis was not observed in the surgical specimen, whereas in 29 (32 per cent) metastasis to lymph nodes was demonstrated (Table III). It is important to note, however, that the presence of metastasis was not necessarily of fatal significance. This nodal relationship was fairly constant whether the cancer was located in the proximal or distal segment and whether the stomach was partially or completely resected.

What is the prognosis for the survivor of gastrectomy for cancer in relation to the presence or absence of metastasis to lymph nodes? Of the resection survivors with negative nodes, 44.0 per cent remained free of cancer for 5 years or longer and only 14.8 per cent of those with positive nodes remained clinically cured. This observation re-emphasized the significance of this factor.

Effect of Location and Distribution of Lymph Nodes.—With the hope of obtaining information regarding the effect of the distribution of lymphatic metastases (Fig. 6), we have divided the material into 4 categories: (1) metastasis to lymph nodes on the lesser curvature, (2) metastasis to lymph nodes on the greater curvature, (3) metastasis to lymph nodes on both curvatures, and (4) metastasis to lymph nodes with location not stated.

Recurrence rate within the 5-year period was extremely high regardless of the location of the involved lymph nodes. However, 16.7 per cent of patients remained free of cancer if only the nodes on the greater curvature were involved by metastatic cancer, as opposed to 8.6 per cent when nodes of both curvatures were involved. Despite this, it is of interest that 4 cases in the latter category survived free of cancer for 5 years.

RELATIONSHIP OF PATHOLOGIC FINDINGS TO FIVE-YEAR SURVIVAL IN PATIENTS WHOSE SURGICAL SPECIMENS SHOWED NO LYMPHATIC METASTASES

The marked difference in 5-year survival after curative resection with and without metastasis to lymph nodes has been demonstrated. A question was posed by the fact that many of those patients without nodal metastases, the more favorable group, died of cancer.

For this evaluation, operative deaths, indeterminate cases, and those patients who died under 5 years of causes other than cancer were excluded. A comparative study was then made of the 62 clinical cures and 68 failures after resection for gastric cancer (all without lymphatic metastases). It was hoped that in this way we might be able to demonstrate the prognostic significance of pathologic features other than the presence or absence of metastasis to lymph nodes (Table IV).

TABLE IV. RELATIONSHIP OF PATHOLOGIC FINDINGS TO 5-YEAR SURVIVAL IN PATIENTS WHOSE SURGICAL SPECIMENS WERE LYMPH NODE NEGATIVE

PATHOLOGIC FINDINGS	SUCCESSFUL RESECTIONS	UNSUCCESSFUL RESECTIONS
All cases	62	68
Size of tumor		
Less than 6 cm.	44.9	33.6
More than 6 cm.	50.6	58.9
Not stated	4.3	7.5
Gross type		
Borrmann I and II	67.0	38.3
Borrmann III and IV	33.0	61.7
Invasion of serosa		
Present	39.0	50.0
Absent	61.0	50.0
Microscopic grade		
I and II	57.2	35.3
III and IV	33.3	54.4
Ungraded	9.5	10.3

Size of tumor: The size of the tumor seemed to play a relatively important role. There was a slightly greater proportion of cancers larger than 6 cm. in the unsuccessful group, however.

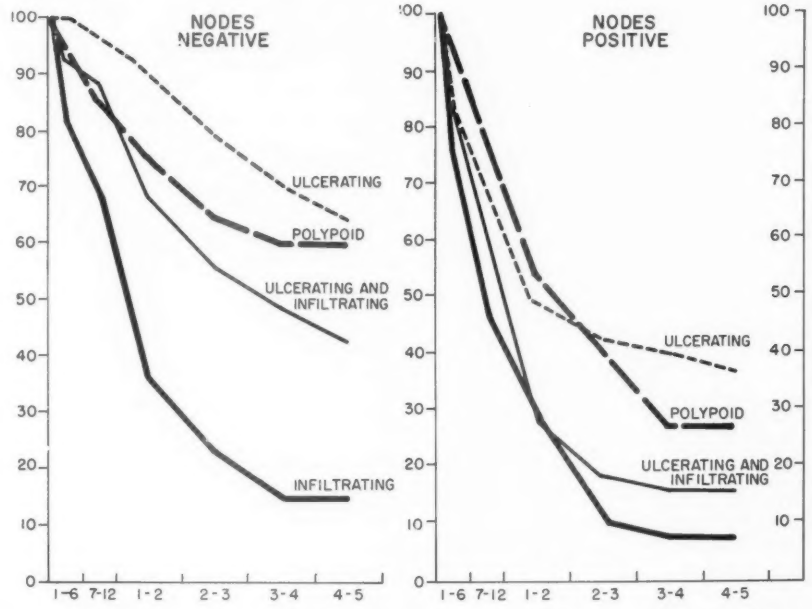

Fig. 7.—Postoperative survival in relation to gross characteristics of the tumor.

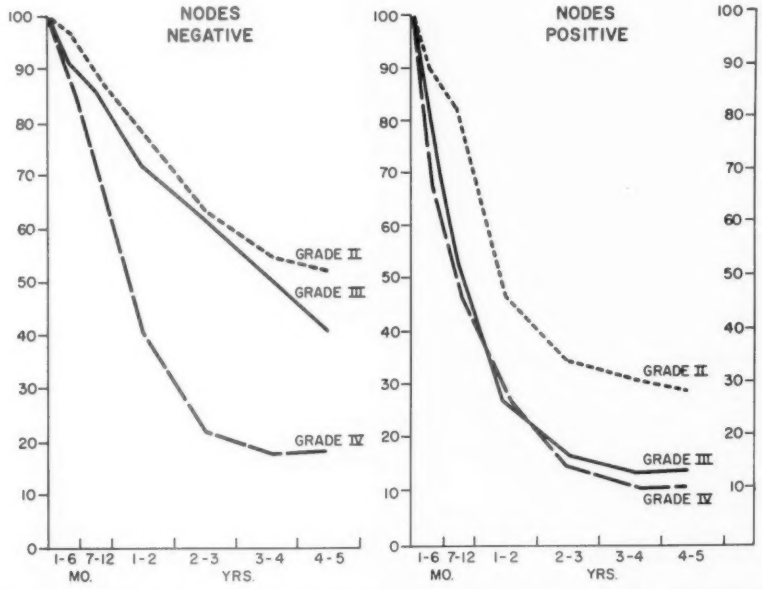

Fig. 8.—Postoperative survival in relation to microscopic grade of the tumor.

Gross characteristics of the tumor (Borrmann classification): In the group of cured cases, there were twice as many lesions classified as Type I and II, as compared to Type III and IV. In the group of patients who died, this proportion was reversed. Fig. 7 graphically demonstrates the importance of the gross

type of the tumor on prognosis when lymphatic spread has not occurred. It is apparent from the survival curves of those patients who had metastasis to lymph nodes that this factor was the predominant one.

Invasion of serosa: The presence or absence of serosal invasion suggests a correlation between depth of invasion and prognosis. Serosal invasion was absent in 61 per cent of the successful resections and present in 39 per cent. In the failures, the presence or absence of invasion of the gastric serosa occurred in equal proportions.

Microscopic grade of tumor: Convincing evidence of the importance of microscopic grade of the tumor is seen in Fig. 8, which graphically portrays the course of the patients who had no metastasis to lymph nodes in the surgical specimen. The presence of lymphatic spread is probably of greater prognostic significance than the microscopic grade, as judged by the smaller variation in the survival curves of the various grades when lymphatic metastases were present.

RELATIONSHIP OF PATHOLOGIC FINDINGS TO FIVE-YEAR SURVIVAL IN PATIENTS WHOSE SURGICAL SPECIMENS SHOWED LYMPHATIC METASTASES

The pathologic findings were reviewed in 29 patients who were cured of their gastric cancer despite the presence of lymphatic metastasis in their surgical specimens. Comparisons were made with observations on 167 patients in the same clinical category who died of cancer within the 5-year period post-operatively (Table V).

TABLE V. RELATIONSHIP OF PATHOLOGIC FINDINGS TO 5-YEAR SURVIVAL IN PATIENTS WHOSE SURGICAL SPECIMENS SHOWED LYMPHATIC METASTASES

PATHOLOGIC FINDINGS	SUCCESSFUL RESECTIONS	UNSUCCESSFUL RESECTIONS
All cases	29	167
Size of tumor		
Less than 6 cm.	41.3	41.9
More than 6 cm.	58.6	54.5
Not stated		3.6
Gross type		
Borrmann I and II	51.9	23.4
Borrmann III and IV	48.1	76.6
Invasion of serosa		
Present	44.8	61.1
Absent	55.2	38.9
Microscopic grade		
I and II	51.9	24.0
III and IV	48.1	70.1
Ungraded		5.9

If lymphatic metastases were present, the extent of their spread probably had a greater effect on the success or failure of the resection than the pathologic characteristics of the lesion itself. The survival curves of the group with nodal metastases, both for gross classification (Borrmann) and microscopic grading (Broders) support this assertion (Figs. 7 and 8). Grouping the patients for 5-year statistics in relation to these various findings shows that other pathologic features may be of some prognostic importance.

DURATION OF LIFE AFTER DIAGNOSIS OF GASTRIC CANCER IN ALL PATIENTS

For estimation of prognosis the 5-year survival rates for various groups give much valuable information but not all the answers, however. The effectiveness of treatment in terms of prolonging life is graphically demonstrated in Fig. 9.

Inoperable Patients.—Since surgery is the only hope of cure for the patient with gastric cancer, all patients who were "inoperable" expired as a result of continued growth of cancer. How long a survival can one expect when the gastric cancer is not amenable to surgery? Within 3 months 62.6 per cent of the patients were dead and in 6 months 83.6 per cent were lost. At the end of one year, 96.1 per cent of the patients had expired as a result of their carcinoma. The course of these patients gave us a base line or yardstick for evaluation of the operable patients.

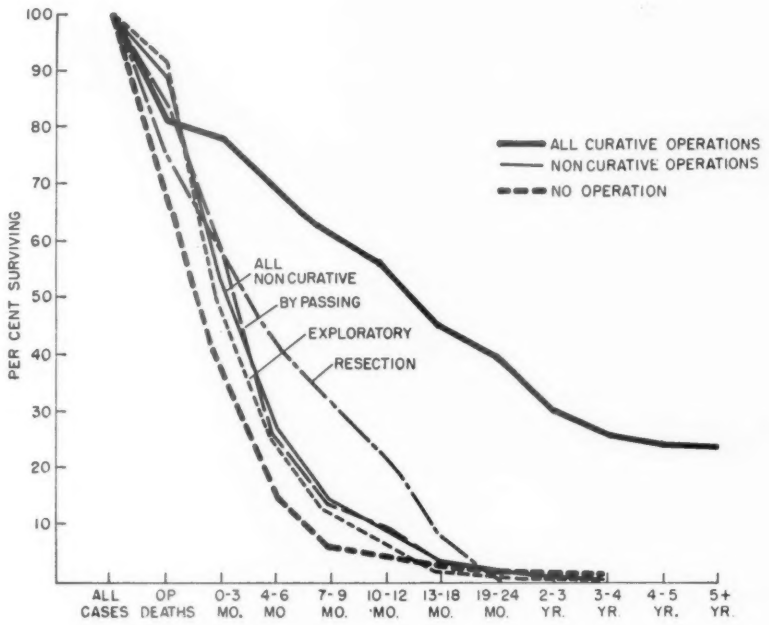

Fig. 9.—Duration of life after diagnosis.

Operable but Incurable Patients.—For those patients who underwent exploratory operations and were found to be incurable, the outlook was much the same as with inoperable patients, unless the local lesion was resected. In the group of patients in whom a palliative gastric resection was carried out, 45 per cent were dead within 6 months, as opposed to 58 per cent of those who underwent exploration without resection. At the end of one year 76 per cent of the patients who were submitted to noncurative resection were dead of cancer while 91.8 per cent of those who had had simple exploration succumbed. Patients subjected to nonresectional operations (bypass operations) had survival curves that were very similar to the groups that were inoperable or subjected to laparotomy alone.

Patients Who Had Undergone Curative Operations.—Fig. 9 shows that 24.8 per cent of these patients were alive 5 years after treatment. This included 11 patients who were alive at the 5-year period but later died of cancer. Thus, 10.8 per cent of apparently cured patients died of cancer after the 5-year mark. Most of the therapeutic failures, however, occurred within the first 3 to 4 years following curative resection. A large proportion of patients who have undergone curative resection for gastric cancer may therefore anticipate cure if they have survived this period. The 5-year yardstick for estimation of "cure" would seem to be a practical measurement in assessing end results in this disease.

SUMMARY

This study has shown that the inherent pathologic capacities of each gastric cancer to grow and disseminate bear the greatest impact on the end results. Successful results following the radical surgical treatment of some of the cases which possessed features of unfavorable import must encourage us to give every patient his chance. There can be no question of our ability to offer the hope of cure to increasing numbers of patients if surgery is offered much earlier to those with locally ulcerative or polypoid lesions. If the operations are devised and carried out with the lymphatic spread well in mind, curability may also be extended to those with cancers of the more infiltrative varieties. Until the final solution of this problem has been established, we must emphasize an aggressive surgical approach to the treatment of gastric cancer.

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EMERGENCY SURGICAL TREATMENT OF THE SEVERELY BLEEDING DUODENAL ULCER

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SEVERE bleeding which threatens the life of the patient is the most serious problem the surgeon and internist have to deal with in connection with duodenal ulcer. It would seem that a bleeding vessel which endangers the patient would be logically treated by ligating it, just as one would ligate any other severely bleeding vessel, and taking such additional measures as might be necessary to prevent recurrence of the bleeding. However, there has been a reluctance on the part of many internists and some surgeons in past years to avoid direct surgical treatment; using, instead, such means as rest, dietary restrictions, blood transfusions, and observation with the hope that bleeding would cease. This plan of therapy was used not so much because of satisfaction with medical management as it was because of the poor results obtained with surgical treatment.

The patient who has bled almost to the level of exsanguination is a poor candidate for surgical treatment. He is usually an individual of older age with cerebral, hepatic, and cardiac anoxic impairment which have resulted from the bleeding. If one adds to these hazards the inflammatory edema, deep penetration, and callosity which are common features of the bleeding ulcer, it is not difficult to understand why operative treatment by the generally accepted method of partial or subtotal gastric resection is such a hazardous undertaking.

After reflecting on the satisfactory experience with vagotomy and pyloroplasty in the treatment of less critical duodenal ulcer lesions requiring surgical treatment, it was decided that this simpler form of treatment, suitably modified to deal with the bleeding component, might well be used for the bleeding duodenal ulcer requiring emergency treatment. One of us (J. A. W.) inaugurated a program at the Veterans Administration Hospital, Long Beach, in 1949, in which the bleeding vessel is ligated with a specially adapted transfixion suture, following which a simple pyloroplasty of the Heineke-Mikulicz type is completed and a vagotomy performed. When this program was first adopted, the operation was divided into 2 stages; the ligation and pyloroplasty were performed in the first stage and the vagotomy a week or two later when

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the patient's general condition would be more favorable for the additional procedure. However, one experience in which severe bleeding recurred caused us to change the operation to a single rather than a 2-stage procedure.

The purpose of this paper is to report the results of the combined procedure of vascular ligation, pyloroplasty, and vagotomy in the group of patients with severely bleeding duodenal ulcer on whom operation was performed as an emergency lifesaving procedure.

Thirty patients were treated for massive duodenal ulcer bleeding during the 7 years from 1949 to 1956 covered in this report. All of the patients showed evidence of hypovolemic shock during the bleeding episode. Eighty-five per cent had hemoglobin concentrations of less than 60 per cent of normal, with the average of the entire group showing an initial hemoglobin level of 8.1 Gm. per 100 c.c. Seventy-eight per cent of the patients were over 40 years of age.

The average period of intensive medical therapy prior to operation was 80 hours. The group of 30 patients received an average of 8 units of blood each in the several days before operation. In every instance blood was administered during the operation, frequently into more than one vein.

Of the 30 patients operated upon, 24 had ligation, pyloroplasty, and vagotomy in a single stage. The other 6 patients had ligation and pyloroplasty in the initial operation, with vagotomy contemplated as a later procedure under more favorable conditions.

OPERATIVE PROCEDURE

As soon as the patient arrives in the operating room, a vein at the elbow is exposed and a polyethylene tube is inserted for blood transfusion if the vein cannot be easily entered by needle puncture. Blood transfusion is continuous throughout the operative procedure. A Levin tube is passed through the nostril into the stomach, and the patient is given endotracheal anesthesia with cyclopropane. The endotracheal intubation is a safegard against aspiration of gastric content.

The abdomen is opened through a high transverse abdominal incision which extends just beyond the lateral borders of the rectus muscles. The first portion of the duodenum is exposed, and an incision 6 cm. in length is made through the anterior wall of the pyloroduodenal segment across the pyloric ring. The incision is made slightly longer on the gastric side than on the duodenal side of the ring. Blood which is contained in the stomach and duodenum is quickly aspirated, and the bleeding vessel is located by exposing the base of the ulcer. Retraction to expose the lesion is made with special pyloroplasty hooks or with guide sutures. The bleeding vessel is ligated with No. 30 processed cotton suture on a stout full-curved needle which will not break easily as it is passed through the calloused ulcer base. The ligature is placed in a figure-of-eight manner deeply down to the pancreas in order to make certain that the vessel is securely ligated. A favorable change in the patient's condition is usually evident as soon as the bleeding is arrested.

The pyloroplasty is now completed by making a single row closure of the pyloroduodenal incision in a transverse direction. There need not be immediate concern as to whether or not the pyloroplasty provides an adequate outlet. The object is to save the life of the patient, and if the pyloric outlet proves to be inadequate in the following days, a gastrojejunostomy may be added when the patient's general condition is improved.

A subdiaphragmatic vagotomy is now performed according to the method of Dragstedt, in which the esophagus and vagus nerves are brought from the lower mediastinal area into the abdomen through the esophageal hiatus and the vagus nerves are divided.

After completion of the vagotomy, the abdominal wall incision is closed. The nasogastric suction tube is left in place to provide aspiration of the gastric contents during the next 5 days. Nothing is given by mouth during this period. Blood is given to restore the loss as indicated by the hemoglobin level during the early postoperative period.

RESULTS

In 24 cases treated by one-stage transfixion ligation, pyloroplasty, and vagotomy, there were no deaths. All of these were emergency operations considered necessary as lifesaving measures. One of the patients required 2 additional operations one and 2 weeks later because of recurrence of bleeding. At the third operation in this patient, a Billroth II gastric resection was performed, with eventual satisfactory recovery. It is our opinion that recurrence of bleeding was due to failure to place the figure-of-eight transfixion suture deep enough at the original operation.

Six other patients were operated upon by ligation and pyloroplasty alone in the early phase of the study, with the idea of adding the vagotomy at a more favorable time. The sixth of these patients had a fatal hemorrhage several days after the ligation and pyloroplasty. Because of this occurrence, it was decided to discontinue the practice of postponing vagotomy, and it is now our practice to complete the ligation, pyloroplasty, and vagotomy in a single operation.

DISCUSSION

The procedure of transfixing ligation in the management of the critically bleeding duodenal ulcer would appear to be as logical as ligation of a bleeding vessel in any other situation, yet it has been generally condemned as being ineffective in this urgent situation. Those who favor vagotomy and pyloroplasty as a means of treating duodenal ulcer surgically have considered the massively bleeding ulcer to be an exception to this form of treatment. It would appear that ligation alone is unsatisfactory because nothing additional is done to reduce the corrosive action of the gastric secretions. With this harmful influence removed by vagotomy, ligation becomes a simple, effective procedure. The results obtained in this group of patients indicate the superiority of this simple method over subtotal gastric resection, which is almost always a prolonged, hazardous procedure under adverse conditions. Even

if bleeding should recur following ligation, pyloroplasty, and vagotomy, as it did in one of our patients, the surgeon may still perform a subtotal gastrectomy at a more favorable time. These results, obtained by a relatively simple procedure when time and simplicity are such important factors, constitute a strong argument for its use in the critical situation of threatened fatal bleeding.

SUMMARY

A procedure is described in which the critically bleeding duodenal ulcer is controlled by ligation of the bleeding vessel, pyloroplasty, and vagotomy. There were no fatalities in a group of 24 patients in whom this surgical procedure was performed in one stage. One of the patients in the group required 2 additional surgical procedures because of recurrence of bleeding.

In 6 cases, the operation was limited to ligation and pyloroplasty in the initial stage, with vagotomy to be performed at a more favorable time. One of these patients died of a recurrent hemorrhage without vagotomy having been added, and it was then decided to make a practice of combining the 3 procedures of ligation, pyloroplasty, and vagotomy in a single operation.

The results indicate that ligation, pyloroplasty, and vagotomy combined in a single operation is a simple, effective means of dealing with the actively bleeding ulcer which threatens the life of the patient.

OPERATIONS FOR NEW PRIMARY NEOPLASMS OVER FIVE YEARS AFTER TOTAL PELVIC EXENTERATIONS FOR ADVANCED PELVIC CANCER

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(From the Memorial Center for Cancer and Allied Diseases)

A NUMBER of reports have appeared in the literature recording instances of multiple primary malignant tumors in one individual arising from one organic system or in more than one organic system. The emphasis in these reports has been to demonstrate that there may be a veritable "carcinoma tendency" in some individuals.

The purpose of this report is to record 3 instances of total pelvic exenteration for advanced cancer of the pelvis in which there was survival for 5 years and then development of a second neoplasm in another organic system necessitating additional operative procedures. In 2 instances total pelvic exenteration was carried out for carcinoma of the cervix that involved bladder and rectum and in one instance total exenteration was performed for recurrent cancer of the corpus uteri involving the bladder and rectum. The second development of neoplasms necessitating further major surgical procedures included a carcinoma of the breast, a hypernephroma of the kidney and, a cystadenoma of the pancreas.

CASE REPORTS

CASE 1.—E. M., a 59-year-old woman, was admitted to the hospital on Dec. 23, 1948. Fifteen years previously she had received radium application to the cervix for epidermoid carcinoma (verified biopsy). For the past 6 or 7 months she had noted vaginal discharge for which douches were taken, and shortely before admission urine had been noted to escape from the vagina.

Pelvic examination revealed a large ulcer replacing the cervix with induration extending into the bladder base and a vesicovaginal fistula through the cancer. There was also induration extending backward along both uterosacral ligaments and obvious involvement of the rectum.

Dec. 30, 1948, total pelvic exenteration was carried out. The right ureter was enlarged and obviously obstructed by the extensive cervical cancer. During the operation the right ureter fractured in its lower third and purulent fluid escaped from the upper segment. Since preoperative pyelograms showed right hydronephrosis and since the right ureter was thickened and friable, it was deemed preferable to carry out a right nephrectomy. Exploration of the upper abdomen was negative except for cholelithiasis and thickened gall-bladder wall. A wet colostomy was constructed with left ureterocolic anastomosis.

Convalescence was complicated by an attack of acute pneumonitis and she was discharged on Feb. 6, 1949, the thirty-eighth postoperative day.

The recording of the data herewith presented was facilitated by a grant from the James S. and Marvelle Adams Foundation, Greenwich, Conn.

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Follow-up visits during the years 1949 to 1956, inclusive, revealed rather prompt return to full activity and excellent adjustment to the wet colostomy. However, there were brief periods of dyspepsia and also brief attacks of right upper quadrant pain radiating to the back and right shoulder. On occasion a local physician was called who administered morphine.

On July 15, 1956, she was admitted to the hospital complaining of severe epigastric cramps, nausea, and vomiting. There was minimal abdominal distention. The impression was acute cholecystitis. She was discharged 6 days later.

On April 4, 1957, the patient was re-admitted because of attacks of upper abdominal pain recurring at times after meals.

On April 9, 1957, the upper abdomen was entered through a high midline incision. The gall bladder, whose walls were quite thick and which contained numerous small concretions, the largest about 1 cm. in diameter, was excised in the usual retrograde manner. On further palpation there was a spherical mass discovered bulging outward from the anterior surface of the mid-portion of the body of the pancreas. It measured 2 by 1.5 by 1 cm. When directly exposed as a result of downward retraction of the stomach and transection of the gastrohepatic ligament, it was found to consist of closely applied transluscent locules, with an appearance typical of cystadenoma of the pancreas. By blunt dissection it was excised intact from pancreatic tissue. The defect in the latter was closed by interrupted silk sutures and the abdomen was closed with soft rubber drains to the gall-bladder bed and excision site in the pancreas.

Histologic study of the pancreatic tumor confirmed the diagnosis of cystadenoma (benign in this case).

The patient was discharged on the seventeenth postoperative day. Clear pancreatic juice was discharged from the drain site for several days after she left the hospital, but this ceased about 10 days later. The patient has been clinically well since her discharge from the hospital (Fig. 1).

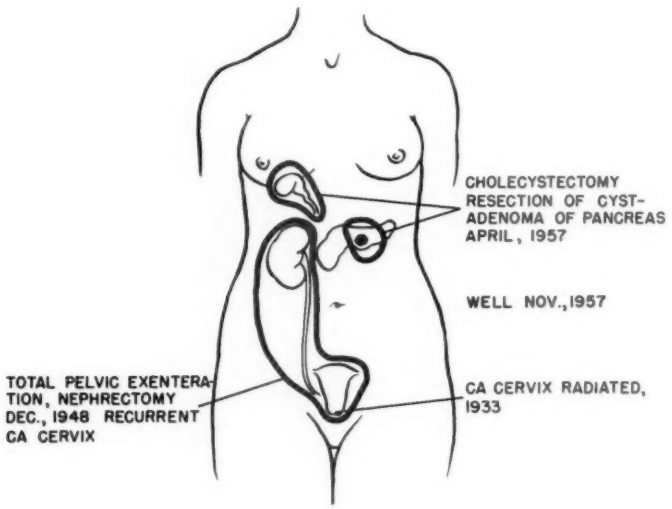

Fig. 1.

Case 2.—R. B., a 63-year-old woman, presented with a history of vaginal bleeding 2½ years ago and a diagnosis of endometrial carcinoma made elsewhere. This was treated by radium locally and x-rays to the pelvic portals. Nine months prior to the present admission, there was recurrence of vaginal bleeding and a panhysterectomy was performed. Two months prior to this admission vaginal bleeding again recurred. Fifteen x-ray treatments were given. On pelvic examination a smooth rounded mass about 4 cm. in diameter was found at the site of the uterus. Biopsy of the vaginal vault revealed adenocarcinoma. On vaginal examination carried out under anesthesia, the mass was entered by digital palpation and reddish fluid

contents were evacuated. The anterior wall of the space evacuated was formed by the bladder, and the posterior wall was formed by the rectum. Histologic study of the evacuated material showed adenocarcinoma.

On Dec. 3, 1949, a total pelvic exenteration was carried out with formation of a wet colostomy. The pathology report showed adenocarcinoma on the posterior bladder wall and vault of the vagina. The lower anterior rectal wall showed "granulomatous inflammation." It would have been impossible at operation to separate the lower anterior rectal wall and excise widely the mass of semisolid recurrent tumor.

Convalescence was complicated by complete wound disruption on the sixth postoperative day, at which time a transverse diverting colostomy was made in the transverse colon (to protect the ureterocolic anastomosis). The colostomy was closed 39 days later. She was discharged 57 days after the exenteration.

The patient was seen at rather frequent intervals during the 7 years following operation and her general status remained very good. Adjustment to the wet colostomy was excellent. There is some hydronephrosis on the left and probably nonsignificant distortion of calyces on the right. During the early months of 1957, discharge of bright red blood from the wet colostomy was noted at intervals but there were no other objective signs of disease. A barium enema was reported negative.

On July 17, 1957, during the course of a follow-up visit, a poorly defined hard mass 2.5 cm. in diameter was discovered in the upper outer quadrant of the left breast. Excisional frozen section biopsy was reported as duct carcinoma and a left radical mastectomy carried out. Study of the whole specimen revealed metastases in one axillary node. Convalescence from the radical mastectomy was complicated by a period of sudden hypotension 6 hours after operation (172/86 to 100/60). The diagnosis of acute anterolateral myocardial infarction was made by electrocardiography. Two hours after this episode the blood pressure returned to normal. She was kept on bed rest for 2 weeks and discharged on the seventeenth postoperative day. Three months later she remains well and is quite active (Fig. 2).

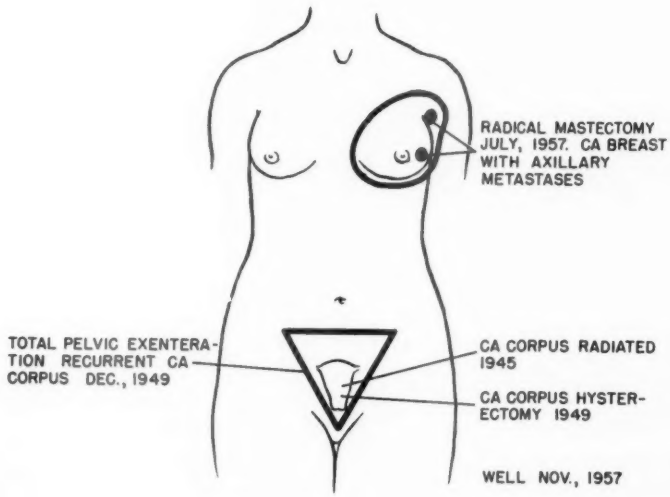

Fig. 2.

CASE 3.—J. C., a 44-year-old woman, was first seen by me in consultation in another hospital. At the time she was bedridden, extremely cachectic, and was being treated by x-ray to the pelvic portals for an advanced ulcerating carcinoma of the cervix that had produced a vesicovaginal fistula. The rectal colon seemed involved.

On July 3, 1952, a total pelvic exenteration with wet colostomy was carried out. Pathologic study revealed extensive invasion of the bladder, parametria, ulceration of the rectal colon, and involvement of both ureters. Interestingly enough the pelvic nodes were free of

metastases. Convalescence was complicated by left leg thrombophlebitis. She was discharged on the thirty-third day. Eventual return to full activity ensued with excellent adjustment to the wet colostomy within a few months.

During the spring and summer of 1954, there were bouts of pyelonephritis which were readily controlled by Gantrisin. On July 5, 1954, an enlargement of the left kidney was present. Roentgenograms confirmed this finding. At the time it was felt that this represented hydronephrosis. The patient was not cooperative and refused frequent visits. By December, 1954, the mass had not increased in size, but the patient had become conscious of its presence. During 1955 the mass slowly increased in size until April, 1957, when it had more than doubled in size since its first detection. By this time she consented to hospitalization and on May 7, 1957, a left nephrectomy through a left lateroabdominal incision was carried out. As soon as the mass was exposed it was obvious that it consisted of a hypernephroma involving the left kidney and that there were periaortic node metastases. The latter were also excised as extensively as possible.

Immediate recovery from the operation ensued, but shortly thereafter severe back pain was found to be due to vertebral metastases and later pulmonary metastases developed. Cachexia was progressive and severe decubiti developed over the sacral region. She expired Nov. 6, 1957. Necropsy was not permitted. There was no clinical evidence nor evidence at the last operation for nephrectomy that the first cancer of the cervix had recurred (Fig. 3).

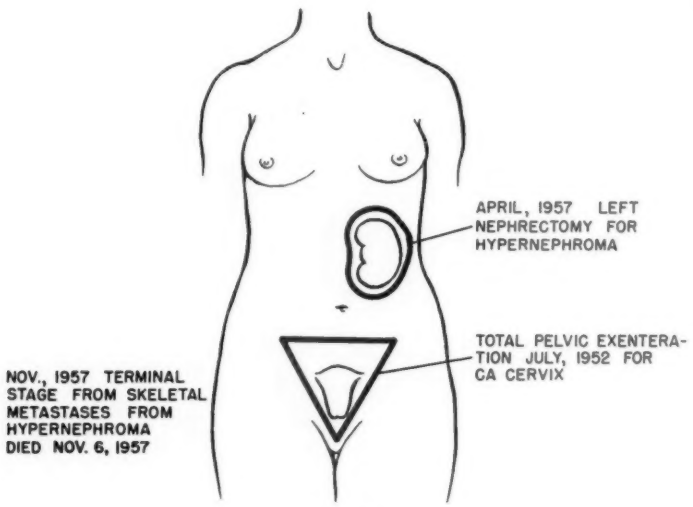
APRIL, 1957 LEFT NEPHRECTOMY FOR HYPERNEPHROMA
TOTAL PELVIC EXENTERATION JULY, 1952 FOR CA CERVIX
NOV., 1957 TERMINAL STAGE FROM SKELETAL METASTASES FROM HYPERNEPHROMA DIED NOV. 6, 1957

Fig. 3.

DISCUSSION

The total pelvic exenterations were successful in controlling the advanced cancers in the pelvis of all of these patients for at least 5 years.

In 2 instances the lesions necessitating total pelvic exenteration were epidermoid carcinomas of the cervix and in one an adenocarcinoma of the corpus.

The development of a second primary benign or malignant neoplasm necessitating operation after successful control of a previously excised malignant neoplasm is not an unusual clinical experience. As methods of treatment improve in their efficiency, the incidence of subsequent development of neoplasms necessitating second or even more attempts to control them will increase. There is ample accumulating evidence for the constitutional tendency for neoplasia.

Pelvic exenteration is a very radical procedure necessitated by an advanced stage of a pelvic neoplasm. The radicality of this operation and its eventual success in long-range control of the cancer in question should not because of its success allay vigilance in continued follow-up of the patient and continued search for developing neoplasms elsewhere in the body and eventual aggressive attack upon them. The 3 instances of this situation described emphasize this principle.

EXPERIMENTAL LIGATION OF THE INTERNAL MAMMARY ARTERY AND ITS EFFECT ON CORONARY OCCLUSION

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IN RECENT reports from Italy enthusiasm has been expressed by Battezzati and associates[1] for ligation of the internal mammary artery in the treatment of coronary arterial insufficiency. In this country Glover and others[3] have been interested in this procedure and have advocated its use. Their results apparently have been sufficiently gratifying to permit them to continue to employ this method in patients with myocardial ischemia. Despite the successful clinical results which have been reported, skepticism remains in the minds of many regarding the value of this procedure.

Although anatomic studies in both man and the experimental animal have shown the presence of small vascular communications between the internal mammary artery and the coronary circulation, little work has been done in the experimental laboratory to evaluate quantitatively the volume of flow through these channels. Furthermore, there is inadequate information available concerning the effects of ligation of the internal mammary artery on the protection offered the heart against experimentally induced ischemia. The purpose of the present study has been to evaluate in the experimental animal the volume of blood flowing through the internal mammary artery after acute and chronic ligation and to study the role of this procedure in protection of the heart subjected to ligation of a major coronary artery.

METHOD

A total of 47 dogs was used. These animals were divided into 3 groups. All animals were anesthetized with endotracheal ether and maintained on positive pressure respiration. In Group I 9 animals were used (average weight of 9.9 Kg.). A left thoracotomy was performed, and the left subclavian artery was exposed and its internal mammary branch was ligated in the second intercostal space. All other branches of the subclavian artery were ligated at their origins (Fig. 1). Heparin (30 mg.) was then administered intravenously. The left subclavian artery was ligated distal to its internal mammary branch and a polythene catheter was passed into this end of the vessel and connected to a calibrated burette as illustrated in Fig. 2. This system was attached to a constant pressure chamber, permitting the burette to be exposed to the pressure

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*Investigator, Howard Hughes Medical Institute.

desired by control of a mercury manometer. Aortic arterial pressure was constantly recorded by means of a catheter passed through a femoral artery and attached to a strain gauge. The burette was filled with blood by permitting blood to flow into it from the subclavian artery. This blood could then be subjected to the prevailing mean aortic pressure and perfused into the internal mammary artery during temporary occlusion of the left subclavian artery at its origin with an arterial clamp. By use of a stop watch, blood flow into the

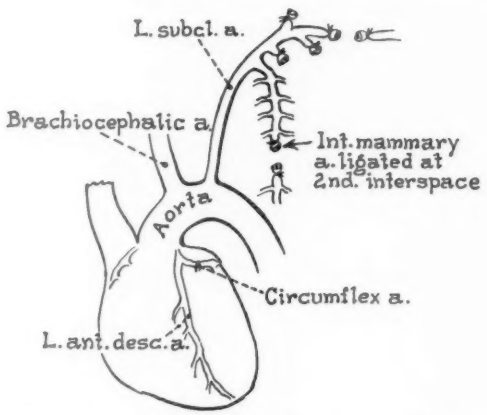

Fig 1.—Diagrammatic illustration of ligation of internal mammary artery and branches of the subclavian artery.

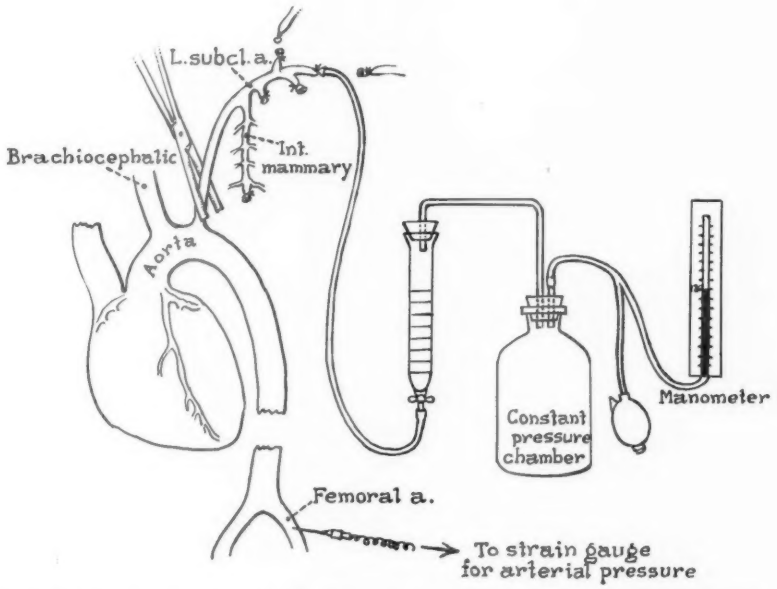

Fig. 2.—Diagrammatic illustration of method employed to determine volume of internal mammary blood flow.

internal mammary could be accurately measured. The backpressure in the internal mammary artery was determined by a strain gauge and backflow was determined by retrograde flow into a small calibrated cylinder. Protamine sulfate (30 mg.) was then given intravenously to counteract the heparin. Following this the anterior descending coronary artery was dissected, ligated, and divided at its origin from the left coronary artery, and the chest was closed.

In Group II 15 animals were used (average weight of 9.2 Kg.). They were first subjected to bilateral extrapleural ligation of the internal mammary arteries in the second intercostal space. These animals were observed for a period of time (average of 33 days), and the left chest was then opened and a polythene catheter was introduced as in the Group I studies. The other branches of the subclavian artery were ligated and internal mammary flow was determined (Fig. 2). In other words, blood flow was measured under these circumstances in animals in which the internal mammary artery had been ligated sometime previously, permitting time for possible compensatory changes to occur. At the completion of the flow studies the anterior descending coronary artery was ligated at its origin and the chest closed.

In Group III 13 animals were used (average weight of 8.8 Kg.). In these animals a left thoracotomy was performed similar to that in Group I and II with ligation of the internal mammary artery in the second intercostal space. In addition each of the other branches of the subclavian artery was ligated at its origin. After an observation period (average of 46 days) the left chest was re-entered and flow in the internal mammary artery was determined by the method previously described. The anterior descending coronary was ligated and divided and the chest closed.

At the completion of some of the experiments in each of the 3 groups, India ink was injected into the internal mammary artery in an effort to demonstrate communication with the coronary arterial system. Sections of the heart were taken for microscopic study and stained with hematoxylin and eosin. These studies were compared with similar injections in normal control preparations. In a separate group of 10 animals, a left thoracotomy was performed and the anterior descending coronary artery was ligated and divided at its origin for use as controls.

RESULTS

In Group I blood flow in the internal mammary artery was determined immediately after ligation of this vessel in the second anterior intercostal space. Under these circumstances blood entering the internal mammary artery from the subclavian artery flowed out into the branches proximal to the second intercostal space ligature. The average mean aortic pressure at the time of study was 103 mm. Hg and the mean perfusion pressure in each instance was equal to the mean aortic pressure. The average blood flow was found to be 2.7 c.c. per minute with a backflow of 0.5 c.c. per minute and a backpressure of 43 mm. Hg. Following ligation of the anterior descending coronary artery, 78 per cent of the animals died (Table I).

In Group II blood flow in the internal mammary artery was determined after *chronic* ligation of this vessel in the second anterior intercostal space. After an average observation period of 33 days, the flow in the internal mammary artery was measured using a perfusion pressure equal to the mean pressure in the aorta (average of 105 mm. Hg). Flow was found to be 2.9 c.c. per minute. The backflow was 0.8 c.c. per minute and the backpressure 48 mm. Hg. Following ligation of the anterior descending coronary artery, the mortality rate was 93 per cent.

TABLE I. BLOOD FLOW AND PRESSURES IN INTERNAL MAMMARY ARTERY

GROUP*	NUMBER OF ANIMALS	AVERAGE WEIGHT (KG.)	AVERAGE PERIOD OF OBSERVATION	PRESSURE (MM. HG)	FLOW (C.C./MIN.)	BACKFLOW (C.C./MIN.)	BACKPRESSURE (MM. HG)	MORTALITY† (PER CENT)
Group I	9	9.9		103	2.7	0.5	43	78
Group II	15	9.2	33	105	2.9	0.8	48	93
Group III	13	8.8	46	97	10.0	9.5	73	92

*Group I: acute study (acute ligation of internal mammary artery); Group II: chronic study (bilateral extrapleural ligation of internal mammary arteries); and Group III: chronic study (ligation of internal mammary artery and concomitant ligation of other branches of subclavian artery at origin).

†Mortality rate following ligation of anterior descending coronary artery.

In Group III all branches of the left subclavian artery were ligated at their origins except the internal mammary artery and this vessel was ligated in the second intercostal space. Under these circumstances the only exit of blood entering the left subclavian artery from the aorta was through the branches of the internal mammary artery proximal to its ligature. In other words, there existed a favorable condition for the development of collateral circulation. After an average observation period of 46 days, blood flow in the internal mammary artery was found to be 10.0 c.c. per minute with a backflow of 9.5 c.c. per minute and a backpressure of 73 mm. Hg. Following ligation of the anterior descending coronary artery, 93 per cent of the animals died.

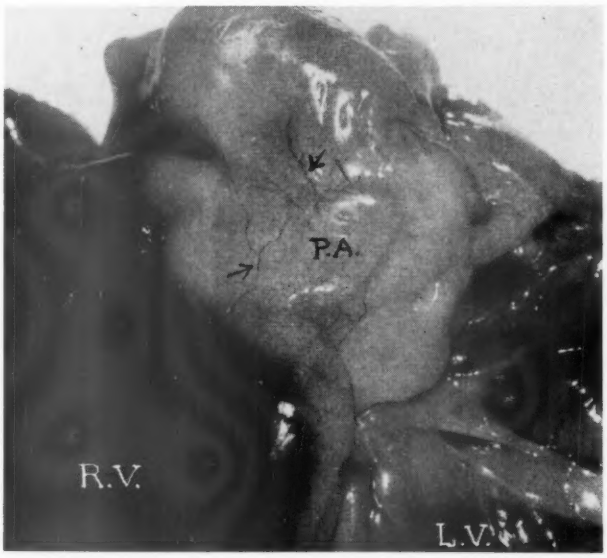

Fig. 3.—Photograph of pulmonary artery and aorta showing small arterial channels on surface filled with India ink following injection of the left internal mammary artery (control animal).

In the control groups of animals subjected to ligation of the anterior descending coronary artery at its origin, the mortality was 70 per cent. Injection studies of the internal mammary artery with India ink showed the presence of small communicating arteries along the aorta, pulmonary artery, venae cavae, and pulmonary veins (Fig. 3). Little difference was noted on gross

examination between the controls and the animals in Groups I and II (Fig. 4). In Group III the mediastinal branches of the internal mammary artery were slightly more prominent. In the microscopic sections India ink was present in the small arteries along the great vessels, while only small traces could be seen in the coronary arteries within the heart.

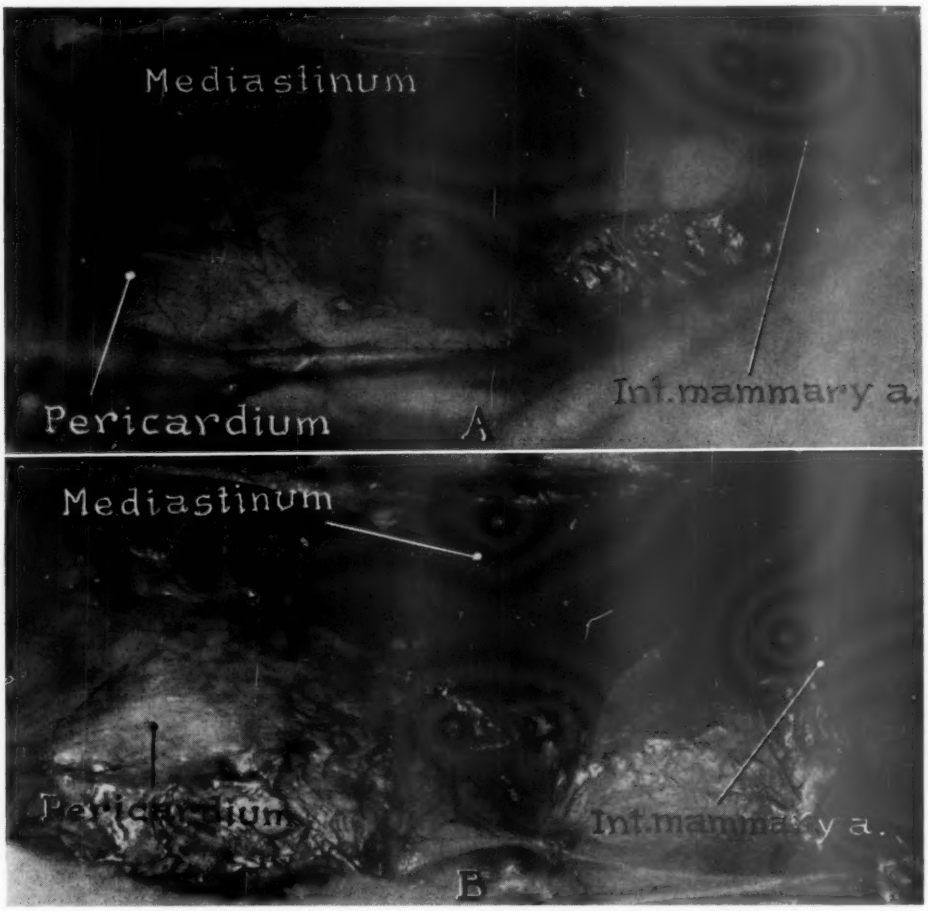

Fig. 4.—*A*. Photograph of control animal showing pericardium and mediastinum following injection of India ink into the internal mammary artery after acute ligation in the second intercostal space (as observed through a left thoracotomy). *B*. Similar photograph in animal with ligation of the left internal mammary artery 46 days prior to injection. There is little observable difference.

DISCUSSION

Extracardiac anastomoses of the coronary arteries have been demonstrated by a number of observers. In 1880 Langer[5] described branches of the coronary arteries anastomosing with vessels in the mediastinum, the diaphragm, parietal pericardium, and hila of the lungs. Wearn[6] injected the coronary arteries with India ink and demonstrated filling of small vessels in the ascending aorta. Widespread anastomoses of the atrial branches and the coronary branches to the pericardial fat with the pericardiacophrenic branches of the internal mammary artery and the bronchial anterior mediastinal vessels also have been described.[4]

Although these small communications between the coronary and systemic circulations are known to exist, little is known regarding the volume of blood which flows through them. Stimulated by Fieschi's anatomic studies, De Marchi, Battezzati, and Tagliaferro[2] have employed ligation of the internal mammary artery in a number of patients with coronary arterial insufficiency. Their first operations were performed in 1954 and their present series is now quite large. In this country Glover has advocated this procedure, has employed it in numerous instances, and appears to be encouraged by the results.

The experimental studies discussed here were performed in order to measure the quantity of blood flowing through the internal mammary artery following its ligation in the second intercostal space and to determine the role, if any, of such a ligation in protecting the heart against induced ischemia. The results indicate that in the normal dog the volume of blood flow under these circumstances is quite small when measured acutely and was found to average 2.7 c.c. per minute. If one assumed that this entire amount was supplied to the heart, which is not the case, it would constitute only a small fraction of coronary arterial flow. The average backflow from the internal mammary was 0.5 c.c. per minute and backpressure 43 mm. Hg. In animals in which the internal mammary arteries were ligated in the second intercostal space (the technique employed clinically) and then observed for a period, the average flow in the internal mammary was found to be 2.9 c.c. per minute. The backflow was 0.8 c.c. per minute and the backpressure 48 mm. Hg. In other words, there was no indication that an increase occurred in flow or backpressure with the passage of time. Somewhat different results were found in those animals in which the internal mammary artery was ligated in the second intercostal space with concomitant ligation of each of the other subclavian branches at their origin. After a period of observation, flow was determined in the internal mammary artery and found to be 10.0 c.c. per minute with a backflow of 9.5 c.c. per minute and a backpressure of 73 mm. Hg. Thus a definite increase in the flow and backpressure in the internal mammary could be demonstrated. It would appear under these circumstances with chronic ligation of the vertebral, thyrocervical, and distal subclavian arteries that there was a marked development of collateral circulation arising from the proximal internal mammary artery.

In each of the animals in the study the anterior descending coronary artery was ligated at its origin in an effort to determine the protective effects of internal mammary artery ligation on induced myocardial ischemia. The mortality in the experimental animals was as great as that in the control group in which anterior descending ligation alone had been performed. In other words, no protection was demonstrated using this conventional method of assay. Even in the Group III animals in which internal mammary flow was found to be augmented markedly, no increase in survival was found.

Injection of the internal mammary artery with contrast media showed the presence of small arterial channels passing toward the heart along the great vessels, but there was little or no gross evidence that these channels were

significantly increased in the experimental group. Microscopic sections of the great vessels near the heart showed contrast media in small arteries in the adventitia with only traces of dye in the larger arteries of the myocardium.

SUMMARY

The volume of blood flow in the internal mammary artery has been determined following experimental ligation of this vessel in the second intercostal space. The flow was measured immediately after ligation in some experiments and after an interval of weeks in others. The volume of flow was found to be quite small in both groups of experiments with correspondingly low values for backpressure and backflow. Small arterial communications between the internal mammary branches and the perivascular arteries along the great vessels entering the heart could be demonstrated by injection techniques, although no protection of the heart against deliberate ligature of the anterior descending coronary artery was found.

Blood flow in the internal mammary artery was significantly increased in the chronic preparation in those experiments in which concomitant ligation of the remaining branches of the subclavian artery was performed. Despite the increase in flow, backpressure, and backflow consistently observed under these circumstances, no protection appeared to be offered the heart when challenged by ligation of the anterior descending coronary artery.

It is concluded from these studies that the volume of blood flowing through the internal mammary artery following ligation in the second intercostal space is quite small and that the procedure does not protect against experimental coronary occlusion.

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THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS IN THE MENTALLY ILL

A 5-Year Study of 403 Resections

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MODERN civilization demands that the surgical diseases of the insane shall be as carefully treated as those of persons of sound mind. The successful invasion of the cavities of the body by the surgeon has stimulated attempts at operative relief for some of the more or less important phenomena which accompany insanity, and it is worth our while to go over the field occasionally and see to what end the efforts have led and to what extent they have been beneficial.'' These were the introductory words in a paper written by Dr. W. J. Mayo in 1901, reviewing his 18 years of surgical accomplishment upon inmates of the state hospitals in Minnesota.[10] He discussed the conditions prevalent among mental patients which were then amenable to surgical therapy and emphasized the physical and occasional mental improvement which could be accomplished by a modern intelligent approach to their surgical diseases. ''In conclusion,'' he said, ''the insane, from a surgical standpoint, have the same right as the sane—no more, no less.'' Dr. Mayo's words may still be considered a motto for those surgeons who have been interested in extending the accomplishments of modern surgery to the unfortunate occupants of mental institutions. It is of interest, however, that no mention was made in his paper of pulmonary tuberculosis, a disease which has always been extremely prevalent among the insane but for which at that time there was no treatment which could be practicably carried out in mental institutions. Today antibiotics and excisional surgery, our 2 most powerful weapons against tuberculosis, can be applied as readily to the mentally ill as to the sound of mind, and humanitarian and public health considerations demand that mentally ill patients with tuberculosis be given the maximum benefit which can be afforded by their use.

In recent years the mortality rate from tuberculosis in the United States' population has decreased rapidly. In great measure this is due to improvement in sanitation and control of tuberculosis in dairy cattle and dairy products and also to better methods of diagnosis and isolation of active cases and improvement of therapy by antibiotics and surgery. The magnitude of this change can best be illustrated by comparison of the death rates from this disease in the years 1900 and 1954 for which figures are available.[16] The U. S. Public Health Service lists these rates as 174.5 in 1900 and 9.3 in 1954 per 100,000 people.

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These figures represent death rates from pulmonary tuberculosis, which is the most frequent form of the infection and accounts for most of the deaths from this disease. Total death rates for all forms of tuberculosis in 1900 and 1954 were 193 and 10.2 per 100,000 people, respectively. It is probable that tuberculosis will in a relatively short period of time be eliminated as a major cause of death in the general population, provided that all reservoirs of active cases are diagnosed, isolated, and treated. In this regard it has long been known that the incidence of pulmonary tuberculosis in state mental hospital inmates is high because of overcrowded conditions in mental hospitals and the impossibility of enforcing adequate hygienic measures.[3, 4, 7] In the State of Minnesota these patients (and some groups of Indians) represent the last large reservoir of tuberculosis, and it has been felt that by eliminating the potential hazard of spread to other inmates and to the general population tuberculosis could be controlled almost completely and reduced to only occasional cases. With these public health considerations in mind as well as the importance of adequate treatment from the viewpoint of individual patients, a program of treatment was instituted in 1950 at the Anoka State Hospital where the Burns Tuberculosis Unit is located and serves all the mental hospitals within the state. The history of the establishment of this unit has been reviewed previously.[4, 12]

The present report represents a review of the surgical experience obtained from 403 pulmonary resections performed on 338 patients during a 5-year period from July 1, 1952, when tuberculosis therapy at Anoka became a cooperative effort with the Department of Surgery of the University of Minnesota, to June 30, 1957. The emphasis in this study has been on the important surgical complications, their management, and the problems peculiar to the mentally ill. Previous reports by Lewis, Shumway, and Perry have described some of the earlier surgical experience at this institution.[9, 12, 14]

SELECTION OF CASES AND MANAGEMENT OF THERAPY

The patients included here are adult psychotic and mentally defective individuals transferred to Anoka from the 10 mental institutions in Minnesota. They were referred on the basis of positive cultures of gastric washings or suspected lesions on roentgenograms. Upon arrival 6 consecutive cultures of gastric washings were obtained prior to instituting antibiotic therapy. Such cultures were repeated if initially negative chest x-rays strongly suggested the presence of tuberculosis. Subsequently all patients with bateriologically proved tuberculosis and those with typical lesions but consistently negative cultures were placed on antituberculosis medication. The program of antibiotic management is discussed later.

Patients with minimal disease whose lesions regressed progressively within 2 or 3 months after institution of medical therapy and whose lesions eventually disappeared were not considered surgical candidates and continued to receive antibiotics for the duration of their treatment. Patients whose lesions regressed after a few months of antibiotic administration to small and stable nodular residuals without open cavities were operated upon and their lesions excised.

Patients with active endobronchial tuberculosis were not operated upon until these lesions healed. When possible, surgery was also deferred on patients with open cavities until these became smaller, became sealed off from the tracheobronchial tree, or healed leaving only small solid residual foci. Patients were not operated upon with positive gastric cultures at the time of the proposed operation except when their lesions enlarged despite antibiotic treatment and the need for prompt removal of the focus of spread became evident. Patients with far-advanced bilateral lesions too extensive for resection without sacrifice of inordinate amounts of functioning pulmonary tissue were not operated upon and were treated medically. Planigraphy, bronchoscopy, bronchography, and other diagnostic procedures were utilized when indicated in the evaluation of extent of disease prior to operation.

Selection of patients for operation was made as follows. When lesions were small, peripheral in location, and away from segmental and subsegmental bronchi, wedge resections were carried out. When the disease was more extensive and involved one or more segments of a lobe but not the entire lobe, segmental resections were performed wherever possible in order to leave intact as much healthy pulmonary tissue as possible. Care was exercised not to cut across diseased lung. Particular emphasis was placed on this and later microscopic examination of the line of resection of the excised tissue as well as the line of section of the bronchus was made to determine whether the margins were involved. Lobectomy was performed when the majority of the lobe was involved. Tuberculous bronchiectasis was considered a segmental disease and treated by appropriate resection. Pneumonectomy was limited to those patients in whom most of one lung was destroyed and whose opposite lung was relatively uninvolved and displayed adequate function. A large number of the patients had bilateral disease. Most bilateral resections were performed in stages at 3- to 9-month intervals. Only 20 bilateral simultaneous resections were performed, usually on younger patients, when extensive resection was anticipated on either side. Such patients were carefully assessed and only those able to withstand bilateral thoracotomy and transverse sternotomy in addition to the resections were managed in this manner. The technique has been described by Lewis and Shumway.[8, 14]

The above criteria used in the selection of the operations were not rigid and changes were required for the problems of individual patients. Figs. 1, 2, and 3 illustrate several degrees of lung involvement and their treatment by appropriate resections.

It should be pointed out that thoracoplasty as a primary procedure for the treatment of pulmonary tuberculosis was not used (except in one case) during the period covered by this report but was reserved for those patients in whom at the end of the pulmonary resection the remaining lung was found to be too small to fill the thoracic cavity. For this purpose, "tailoring" thoracoplasty was used in preference to plombage, pleural tents, pneumoperitoneum, phrenic nerve interruption, and other space-filling procedures. Thoracoplasty, as described later, was also used rather frequently for the treatment of complications.

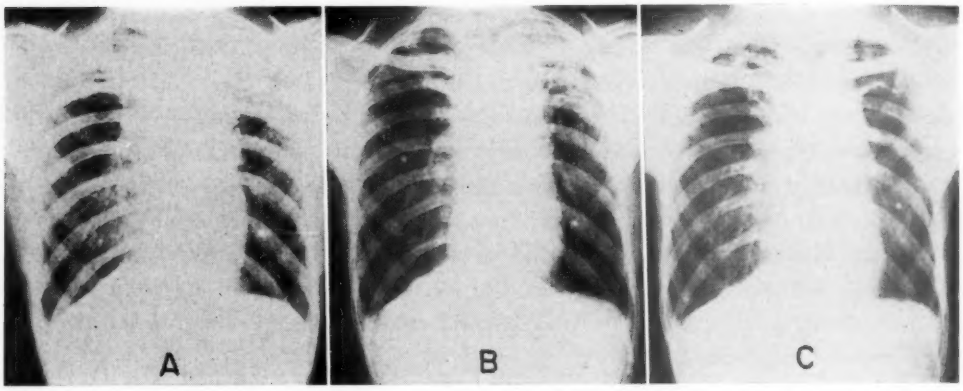

Fig. 1.—Case 1 (E.S.). Roentgenograms showing bilateral staged apical pulmonary resections. *A*, Preoperative film of extensive tuberculous infiltrations of both upper lobes. *B*, Film made 6 months after a right upper lobectomy; the right lung completely fills the right hemithorax. *C*, Seven months following the initial operation a segmental resection of the apical-posterior and anterior segments of the left upper lobe was performed. This film taken one year after the last procedure shows that both lung fields are clear.

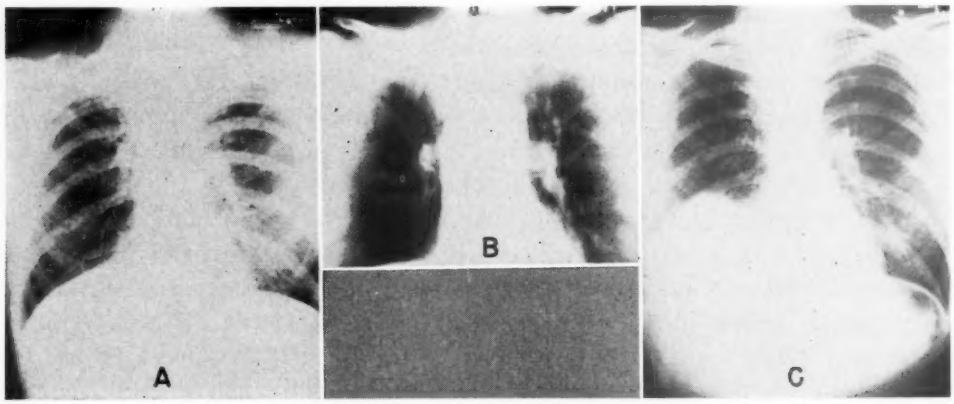

Fig. 2.—Case 2 (E.S.). *A*, Preoperative roentgenograms showing extensive right upper lobe disease with collapse of the en ire apex. *B*, Preoperative planigram also showing the severe involvement of right upper lobe. *C*, Film made 6 months following a right upper lobectomy; the apex is now clear and the remaining right lung fills the entire right chest although the right hemidiaphragm is elevated.

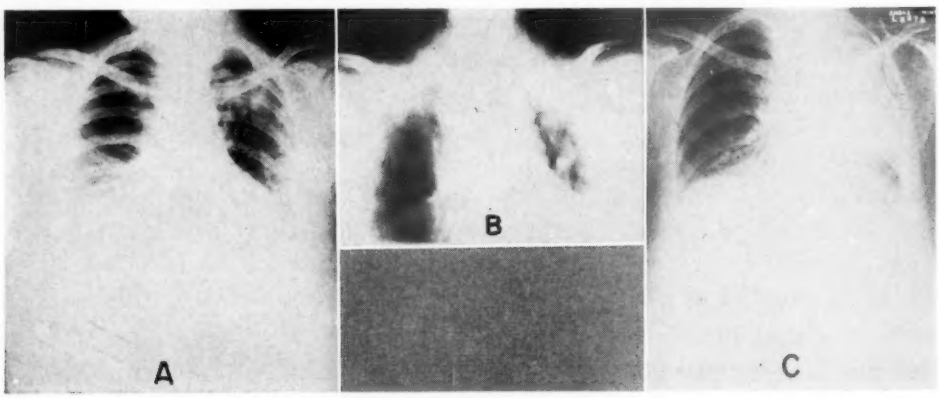

Fig. 3.—Case 3 (C.R.). *A*, Far-advanced involvement of the left lung; a large cavity at the level of the left clavicle. *B*, Preoperative planigram showing the extensive infiltration in the left lung to better advantage. *C*, Roentgenogram made 7 months following left pneumonectomy. The right lung remains clear and uninvolved.

The Use of Antibiotics.—All patients received 200 to 300 mg. of Isoniazid (INH) daily in divided doses and 1 Gm. of streptomycin sulfate intramuscularly twice a week for a total of at least 18 months, a minimum of 6 months of which was received after the last surgical procedure.[6, 15] During the past 2 years with the increasing evidence to support the effectiveness of long-term Isoniazid therapy, this period of antibiotic coverage has been prolonged and patients are maintained on drugs 12 to 18 months following uncomplicated operations. It has been possible to transfer some patients back to the referring institutions for completion of the course. Recently a program of treatment with large doses of INH supplemented by pyridoxine to prevent nervous system damage has been employed in a few selected cases. During the 2 weeks following surgery, the routine therapy was intensified and modified to include 1 Gm. of streptomycin daily in addition to daily INH and penicillin. After recovery from the operation the routine schedule of INH and streptomycin was resumed. Other drugs such as para-amino salicylic acid (PAS), dihydrostreptomycin, viomycin, and pyrizinamide (PZA) singly or in various combinations and dosages were administered with or without INH and streptomycin when drug allergies arose in patients and when specific drug-resistant tubercle bacilli were encountered. The use of INH-streptomycin regimen has been considered the program of choice in these individuals since it is difficult to enlist the cooperation of mental patients in the acceptance of large oral doses of PAS.

RESULTS AND DISCUSSION

Care after thoracotomy in the mentally disturbed has its peculiar problems in addition to those expected in mentally alert patients. These achieved great importance in this series since the group includes many types of psychosis and mental deficiency. Usually these patients are unable to comprehend what is taking place and therefore their active cooperation during the postoperative period is almost nonexistent. Such simple but important voluntary measures as coughing and deep breathing are not possible and must be replaced by endotracheal suction. Tracheotomy was very frequently resorted to as the best method of cleaning the respiratory tree. These difficulties have contributed to the morbidity and to the mortality from the common complications of thoracic surgery.

Types of Operations and Over-all Results.—From July 1, 1952, through June 30, 1957, 338 patients were operated upon. Therefore the results represent follow-up periods of from 5 years to 4 months. Tables I and II summarize the experience obtained in the various types of pulmonary resection. Since 65 patients underwent staged bilateral resections at intervals of several months, a total of 403 procedures were performed and the results have been tabulated accordingly.

The most frequent operation was segmental resection with a total of 289 procedures. In this group there were 10 deaths (mortality rate 3.4 per cent) and 39 complications. All of the latter patients have now recovered except 2 who are at present still under treatment. The next most frequent resections

TABLE I. SUMMARY

TYPE OF OPERATION	NUMBER OF PATIENTS	COMPLICATIONS				
		TOTAL NUMBER	RECOVERED	STILL PRESENT	DEATHS	
Unilateral operations						
Wedge	18	3	1	0	2	
Segmental	159	30	23	1	6	
Lobectomy	53	18	4	1	13	
Pneumonectomy	23	15	8	1	6	
Bilateral operations						
Staged						
Segmental	54	12	9	0	3	
Lobectomy	11	3	1	1	1	
Simultaneous						
Segmental	17	7	5	1	1	
Lobectomy	3	1	0	0	1	
Total	338	89	51	5	33	(9.7%)

The staged bilateral operations each represent 2 operations performed separately. Therefore, total number of operations is 403, giving an over-all operation mortality rate of 8.2 per cent.

TABLE II. OPERATIONS AND OPERATION MORTALITY RATE

OPERATIONS	NUMBER PERFORMED	DEATHS	MORTALITY RATE (PER CENT)
Wedge	24	2	8.3
Segmental	289	10	3.4
Lobectomy	67	15	22.4
Pneumonectomy	23	6	26.1
Total	403	33	8.2

There is a discrepancy between the number of wedge and segmental resections as listed in this table and in Table I. The staged bilateral procedures are listed in Table I only according to the larger resection performed. Table II classifies the total number of operations that have been done.

were 67 lobectomies performed in the unilateral as well as the bilateral cases. Here there were 15 deaths (22.4 per cent) and 7 complications, all but 2 of which have now been treated successfully. The deaths in this group are in the early cases which were desperate ones with bilateral disease. In the last 2½ years only 5 deaths occurred in 38 cases (13 per cent). Pneumonectomy was carried out in 23 patients with 6 deaths (mortality rate 26.1 per cent) with 9 complications resulting. Again, most of these cases represent patients who are considered "salvage" cases such as are frequently not included in series of statistics of elective resections. Only one patient in the pneumonectomy group currently continues to have a complication. There were 24 wedge resections with 2 deaths and one complication. Both of the patients who died had severe postoperative pneumonia; one of them was 71 years old; the other was 59 and had cirrhosis of the liver and coronary and renal arteriosclerosis. In the entire series, there was a total of 33 deaths in 403 operations, giving an over-all operative mortality rate of 8.2 per cent and a patient mortality rate of 9.7 per cent.

Five-rib thoracoplasty for space obliteration was performed at the time of pulmonary resection in 18 lobectomies and 2 segmental resections. In addition to this, total thoracoplasty was performed in 6 of the pneumonectomy cases

prior to resection of the lung, 2 of which were deliberate and in preparation for the forthcoming resection. The other 4 represented failures of thoracoplasty performed prior to the present study.

Postoperative Complications and Their Treatment.—Table I shows that 58 complications (including deaths) occurred in the segmental resection group, 22 in the lobectomy cases, 15 in the pneumonectomies, and 3 in the wedge resections, giving a total of 89 serious complications of which 71 resulted directly from the pulmonary resections and occurred therefore following 17 per cent of the operations. The latter group of complications appear in tabulated form in Table III where it will be noted that bronchopleural fistula with empyema and empyema alone and bacteriologic recurrence or spread of disease account for 46 of them or about two-thirds of the total. The remaining third of the complications consist of incomplete lung expansion, pneumonitis, occult bronchopleural fistula, and atelectasis in decreasing proportion. There were 15 deaths in this group of postoperative complications directly related to surgery, giving a mortality rate of 21 per cent in patients who developed complications. Such complications as were encountered were due to many factors, one of which was resistant organisms. The majority of the complications (that is, 38 cases of incomplete lung expansion, "occult" bronchopleural fistula, empyema, and empyema with bronchopleural fistula), however, appeared to arise in cases wherein the residual lung after resection did not initially fill the chest cavity. When no infection developed, tuberculous or otherwise, in the unoccupied chest cavity, only an area of incomplete lung expansion was seen (7 cases or 1.7 per cent of operations). This space became infected (empyema) in 12 cases or 2.9 per cent of operations and the process progressed further to a frank breakdown of the bronchial stump in a number of instances. This either caused the development of a frank bronchopleural cutaneous fistula (in 16 cases or 3.9 per cent of operations) or an occult bronchopleural fistula at a later date when some healing had taken place (3 cases or less than 1 per cent of operations). An occult bronchopleural fistula as defined by Bell[1] is an asymptomatic postoperative complication wherein an infected space remains in the thorax which communicates with a bronchus. It is best demonstrated by bronchography.

The highest proportion of complications occurred in the pneumonectomy group with 9 complications (mostly empyema) in 23 operations. In one case (Fig. 4, *D*) a bronchopleural fistula developed almost 2 months following pneumonectomy when complete healing was considered to have taken place. This required immediate drainage and eventually a modified Schede procedure.

The treatment used for 38 complications of incomplete lung expansion, empyema, empyema with bronchopleural fistula, and occult bronchopleural fistula was either catheter drainage alone or obliteration of the space by appropriate thoracoplasty. Table III shows that these 2 procedures were sufficient to treat 31 of these cases successfully. Only 4 cases of empyema with bronchopleural fistula required more extensive procedure such as Schede thoracoplasty (one case) and muscle flap procedures to cover the bronchial stumps (3 cases). Of these 38 cases, 33 patients recovered with appropriate therapy, 3 died, and 2 currently still have complications.

TABLE III. POSTOPERATIVE COMPLICATIONS, THEIR TREATMENT AND END RESULT (IN 338 PATIENTS OR 403 OPERATIONS)

TYPE OF COMPLICATION	TOTAL NUMBER	TREATMENT USED					END RESULT		
		CONSERVATIVE OR DRAINAGE	THORACOPLASTY ONLY	DRAINAGE AND THORACOPLASTY	DRAINAGE THORACOPLASTY AND MUSCLE FLEXION	FURTHER PULMONARY RESECTION	COMPLICATIONS STILL PRESENT	RECOVERED	DEAD
B.P.F.* with empyema	16	2	0	10	4†	0	1	13	2
Empyema	12	2	4	5	0	1	0	11	1
Incomplete lung expansion	7	0	7	0	0	0	0	7	0
Occult B.P.F.	3	0	2	0	0	1	1	2	0
Late recurrence or reactivation	10	7	0	0	0	3	2	7	1
Postop. spread	8	6	0	0	0	2	1	5	2
Pneumonitis	12	9	0	0	0	0	0	4	8
Atelectasis	3	2	0	0	0	0	0	2	1
Other (CVA, card. arrest, etc.)	18	—	—	—	—	—	—	—	18
Total	89	28	13	15	4	7	5	51	33

*B.P.F.—Bronchopleural fistula.

†One of these cases required in addition a Schede thoracoplasty.

Postoperative nontuberculous pneumonitis was severe in 12 cases resulting in 8 deaths during the first few weeks after operation.

In the entire series of patients operated upon, there were 10 cases of late recurrence of pulmonary tuberculosis. These represent patients who were previously considered inactive as judged from x-ray findings and negative gastric washings but who later turned up with positive gastric cultures. These 10 cases of late recurrence (or possible reinfection) represent 3.3 per cent of 299 patients treated by surgery and antibiotics (excluding the patients who died and those whose disease progressed further after operation). There have been 8 cases of spread of tuberculosis following operative procedures in the group.

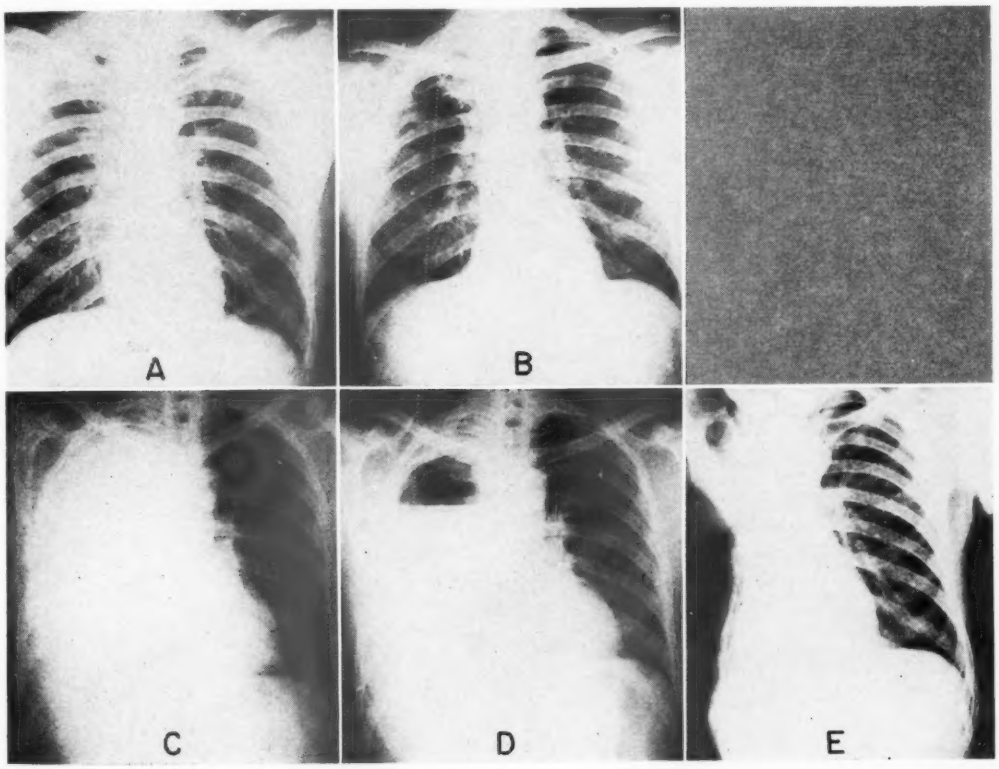

Fig. 4.—Case 4 (P.V.). Late progression and spread of tuberculosis following segmental resection of the right apical region. *A*, Preoperative film showing moderate infiltration in the right apex. *B*, Film made 3 years after a segmental resection of the apical and posterior segments of the upper lobe was performed. Further involvement of the right apical and subclavicular areas may now be seen. *C*, Roentgenogram made 4 weeks after right pneumonectomy; the right hemithorax is filled with fluid. *D*, Seven weeks following pneumonectomy. On this day, the patient suddenly began to cough up old bloody material. This shows an air fluid level not previously seen, indicative of a bronchopleural fistula (B.P.F.) requiring immediate therapy. *E*, Ten months after the onset of the B.P.F. In the intervening period this patient has required extensive total thoracoplasty and a muscle flap procedure. The left lung remains remarkably clear.

Considered together, the 18 cases of recurrence and spread were treated with antibiotics (13 cases) and further pulmonary resection (5 cases); treatment was successful in 12 cases now considered "arrested." Four continue to have positive gastric cultures and 3 have died (Table III).

Of the 71 cases with complications specifically related to the pulmonary resections, 51 patients (71 per cent) recovered after treatment while 5 still

remain under treatment. Figs. 4 and 5 illustrate some of the important complications and the therapy employed.

Analysis of Deaths.—It has been previously noted that there were 33 deaths in the entire group of patients. The causes of death were confirmed by post-mortem examination in all except one and are listed in Table IV. It is noteworthy that 7 patients died during the first week after operation of acute respiratory embarrassment and pulmonary edema. Three of these deaths occurred after pneumonectomy and 4 following lobectomy. The need for accurate preoperative evaluation of pulmonary function by differential bronchospirometric and other studies in cases being evaluated for extensive resection

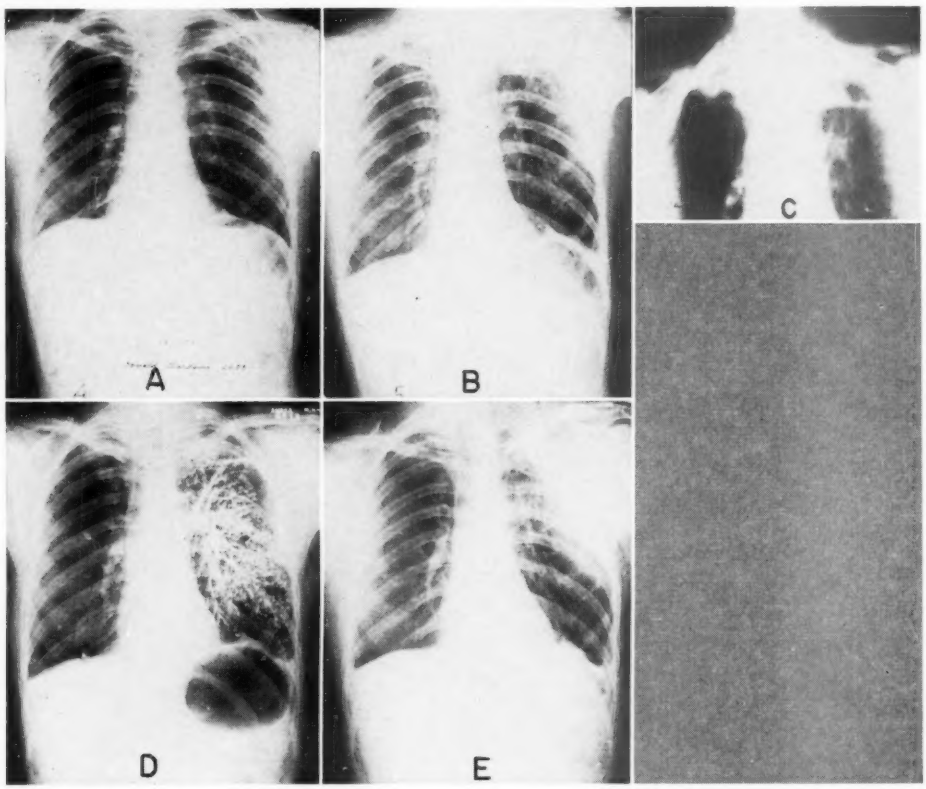

Fig. 5.—Case 5 (D.T.). Illustrating the development of an occult B.P.F. following a segmental resection and its treatment. *A*, Preoperative roentgenogram showing tuberculous infiltration in the left apex. *B*, Film made 7 months following segmental resection of the apical-posterior segment of the left upper lobe, showing air pocket in the left apex. *C*, Planigram with better visualization of air pocket. *D*, Bronchogram showing accumulation of the dye in the air pocket and existence of occult B.P.F. *E*, Film made 5 months following a 5-rib thoracoplasty performed with obliteration of pocket.

is evident; however, the lack of the necessary cooperation on the part of these patients makes such tests almost impossible. Aside from these 7 cases no relationship was evident between the extent of resection and deaths. Table IV shows that the other causes of death are scattered throughout a long list although it is significant that postoperative pneumonitis accounted for 8 deaths. Whereas the over-all operative mortality rate of 8.2 is higher than several reported series of sane patients wherein mortality rates have varied from 3 to 6

per cent,[2, 5, 13] the difference in the present series would seem to be explained by the severity of the disease, the higher age groups of the patients (median age 53 years), as well as the special problems encountered in the care of mentally ill patients.

TABLE IV. CAUSE OF DEATH (IN 338 PATIENTS OR 403 OPERATIONS)

CAUSE OF DEATH	NUMBER OF PATIENTS DEAD DURING: IMMEDIATE POSTOPERATIVE PERIOD (1 WEEK)	NUMBER OF PATIENTS DEAD DURING: LATE POSTOPERATIVE PERIOD (OVER 1 WEEK)	TOTAL NUMBER PATIENTS
Respiratory embarrassment, pulmonary edema	7	0	7*
Pneumonitis (nontuberculous)	4	4	8
Sudden pulmonary embolism	2	1	3
Postoperative spread (tuberculous) and recurrence	1	2	3
B.P.F. with empyema	0	2	2
Cardiovascular accident	0	2	2
Cardiac decompensation	0	2	2
Empyema	0	1	1
Massive pulmonary hemorrhage	0	1	1
Massive atelectasis	1	0	1
Transfusion reaction	0	1	1
Cardiac arrest	1	0	1
Unknown	0	1	1
Total deaths 33 patients	16	17	33

*3 pneumonectomies, 4 lobectomies.

Age Distribution and Severity of Disease.—Most patients sent to the Anoka State Hospital for treatment of tuberculosis had had their disease for many years prior to the initiation of the present program of therapy. Their ages ranged from 18 to 73 years and 50 per cent of them were over 50 years old. The median age of the entire group was 53 years. Twenty-nine of the 33 patients who died were in their fifth to seventh decade of life, a factor which, with the severity of the disease, contributed largely to the mortality rate. In addition to this, 310 patients (91 per cent of the cases) had moderately advanced and far-advanced tuberculosis (Table V) according to National Tuberculosis Association standards.[11]

TABLE V. CLASSIFICATION OF TUBERCULOSIS IN PATIENTS AT TIME OF OPERATION

PULMONARY TUBERCULOSIS CLASSIFICATION	NUMBER OF PATIENTS
Minimal	28
Moderately advanced	237
Far advanced	73
Total	338

Preoperative Bacteriologic Findings and Histologic Picture of Resected Specimens.—At least one series of 6 consecutive gastric specimens were obtained from all patients for culture of tubercle bacilli on laboratory media or for injection into guinea pigs. In Table VI are tabulated the results obtained from these cultures together with the reports of histologic examination of all resected specimens. It will be noted that 294 patients (87 per cent) had positive gastric

cultures at one time during the preoperative period; in 251 of these cases positive evidence of active or healed tuberculosis was found on examination of the specimens, while in 42 cases only "healed scar and inflammation" were seen. It is important to note that although 44 patients had negative preoperative gastric washings, 31 of them had definite evidence of tuberculosis in their excised specimens pointing to the necessity of operation on some selected patients on the basis of the presence of disease seen on chest x-rays alone. At present only 4 patients in the entire group have positive gastric washings. These have resistant organisms or represent reinfection and reactivation cases listed under late complications.

TABLE VI. CORRELATION OF BACTERIOLOGIC DIAGNOSIS AND PATHOLOGY

PREOPERATIVE BACTERIOLOGY	TOTAL NUMBER OF PATIENTS	PATHOLOGIC EXAMINATION OF RESECTED SPECIMENS		POSTOPERATIVE POSITIVE GASTRICS AT PRESENT
		NUMBER WITH POSITIVE EVIDENCE OF TBC	"INFLAMMATION AND SCAR"	
Patients with preoperative positive gastrics	294	251	42	4
Patients with preoperative negative gastrics	44	31	13	0
Total	338	282	55	4

SUMMARY

1. Four hundred and three pulmonary resections were performed on 338 mentally disturbed patients during the period between July, 1952, through July, 1957. Two hundred eighty-nine segmental resections, 67 lobectomies, 23 pneumonectomies, and 24 wedge resections were carried out in unilateral, staged bilateral, and bilateral simultaneous procedures with an over-all operative mortality rate of 8.2 per cent and a patient mortality rate of 9.7 per cent.

2. The most serious postoperative complications are discussed and an analysis is made of their causes and contributing factors. The treatment of these complications is discussed as well as the special difficulties involved in care of mental patients following thoracic operations.

3. At present there are 5 patients with complications; 4 represent postoperative spread and late reactivation, and one has an occult bronchopleural fistula and is awaiting a thoracoplasty.

4. The necessity for operating upon some patients in a group such as this on the basis of radiologic findings alone is demonstrated by the finding of active disease in resected specimens of patients who had never had positive gastric cultures preoperatively.

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LOCALIZED PULMONARY EMPHYSEMA OF INFANCY

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INTRODUCTION

LOCALIZED pulmonary emphysema of infancy is now being recognized with increasing frequency. It presents characteristically as hypertrophic pulmonary emphysema localized to one lobe of the lung with infection, if present, having no relationship to the emphysematous process. An emergency situation may arise from the rapidly progressing lobar distention that may terminate fatally without prompt and proper management. Reports of successful treatment by resection of the emphysematous lobe have made it a condition of practical concern to both pediatricians and surgeons.

A variety of names have been given to the condition including infantile lobar emphysema,[1] tension emphysema in infants,[10] progressive infantile emphysema,[3] localized hypertrophic emphysema,[6, 7, 14, 15, 18] lobar emphysema in infants and children,[4] lobar obstructive emphysema in infancy,[16] and congenital lobar emphysema.[13, 17] In many cases the etiology remains obscure whereas in others it has been attributed to maldevelopment of the bronchial cartilages or redundant folds of bronchial mucosa. It has been found in association with defects of the mediastinum.[5, 9] In several instances it has been associated with bronchial compression by a ductus arteriosus[4] or by pressure from an abnormal vessel.[13] Despite uncertainties concerning its etiology and pathogenesis, the condition does present findings sufficiently characteristic as to warrant its consideration as a distinct entity of infancy. It should not be confused with conditions presenting as areas of localized pulmonary emphysema secondary to partial bronchial obstruction associated with infection, atelectasis, tumors, strictures, or aspirated material. Localized emphysema of infancy also needs to be differentiated from lung cysts, atelectasis with compensatory emphysema, pulmonary agenesis, pneumatocele, diaphragmatic hernia, and pneumothorax.

Four cases of localized pulmonary emphysema of infancy have been treated by surgical resection of the involved lobe at the Buffalo Children's Hospital. In an effort to understand this entity better, our 4 cases have been analyzed along with 36 histologically proved cases gathered from the English language literature (Table I). It must be emphasized that this does not represent an absolute total of all reported cases. An effort has been made to limit the review to cases considered as representative of the entity under discussion. A

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number of cases could not be included in the analysis due to incomplete clinical and pathologic descriptions. For example, insufficient documentation led to uncertainties as to whether a case under consideration truly represented localized emphysema of infancy or a condition closely resembling it such as lung cyst or atelectasis associated with infection and emphysema as described by Caffey.[2] Although a number of cases reported in the foreign literature were reviewed they were not included in the final analysis when it was realized that a complete survey of this literature was not feasible.

TABLE I. CASES INCLUDED IN LITERATURE REVIEW

AUTHOR	NUMBER OF CASES
Bolande (1956)[1]	3
Ehrenhaft and Taber (1953)[3]	3
Fischer et al. (1952)[4]	5
Gross and Lewis (1945)[5]	1
Lewis and Potts (1951)[9]	1
Nelson (1957)[10]	8
Overstreet (1939)[12]	1
Robertson and James (1951)[13]	5
Shaw (1952)[14]	2
Silver et al. (1956)[15]	1
Sloan (1953)[16]	4
White-Jones and Temple (1954)[17]	1
Williams (1952)[18]	1
	36

CASE REPORTS

CASE 1.*—D. S., a white male infant, was born on Aug. 2, 1947, following a normal full-term pregnancy. The delivery was difficult and resuscitation of the baby was said to have been necessary.

On Oct. 23, 1947, he was admitted to the Buffalo Children's Hospital because of progressive respiratory distress and wheezing. Physical examination at that time revealed rapid, shallow respirations with costal retraction. Hyperresonance and decreased breath sounds were noted over the left chest. Chest x-rays taken on admission showed marked emphysematous changes in the left lung with shift of the mediastinum to the right. The bronchoscopist described compression of the left main bronchus which prevented adequate visualization of the left upper lobe orifice.

Because of progressive respiratory distress thoracotomy was performed. On opening the chest the left upper lobe bulged out of the thoracic cavity. After the emphysematous upper lobe was resected, the atelectatic left lower lobe inflated easily. Gross and microscopic examination of the resected specimen revealed the typical findings of hypertrophic pulmonary emphysema with normal-appearing bronchi.

The child's postoperative course was uneventful. When last seen in May, 1957, he had remained asymptomatic except for an occasional upper respiratory infection.

CASE 2.—D. C., a white male infant, was born one month prematurely on Nov. 17, 1953. The gestation and delivery were reported to have been uneventful. Resuscitation was required but details of the method used were not available. Labored respiration and cough were noted the first day. After one week of treatment with oxygen and antibiotics, the dyspnea and cyanosis improved and the infant was discharged.

Two weeks later the dyspnea recurred. A chest x-ray was interpreted as showing atelectasis. The respiratory symptoms progressed and the infant was admitted to Buffalo

*This case has been previously reported in detail by Leahy and Butsch.[8]

Children's Hospital on Jan. 1, 1954. He was well nourished, dyspneic, but not cyanotic. The pulse rate was 142 per minute and respirations 78 per minute. There were absent breath sounds and a resonant percussion note over the right hemithorax. The left side of the chest was dull to percussion. No wheeze or costal retraction was noted. No cardiac murmurs were heard. Laboratory findings were not significant. A chest x-ray was interpreted as showing a large cyst or area of emphysema involving the right lung. The right lower lobe appeared to be compressed. The mediastinum was shifted markedly to the left. Bronchoscopy was cancelled because of rapidly progressing respiratory distress, and an emergency thoracotomy was performed on the day of admission. The right middle lobe bulged out as the pleura was opened. The remaining lung expanded following resection of the emphysematous lobe. The resected lobe did not deflate when allowed to stand with its bronchus open. Scattered small blebs were seen beneath the visceral pleura. Histologically, the typical findings of hypertrophic emphysema were seen with diffuse bleb formation. Occasional areas of recent hemorrhage were apparent, but there was no evidence of infection. The lobar bronchus showed no abnormalities on gross and histologic examination.

The postoperative course was uneventful. The last follow-up visit in May, 1957, showed the child to be asymptomatic and in good health.

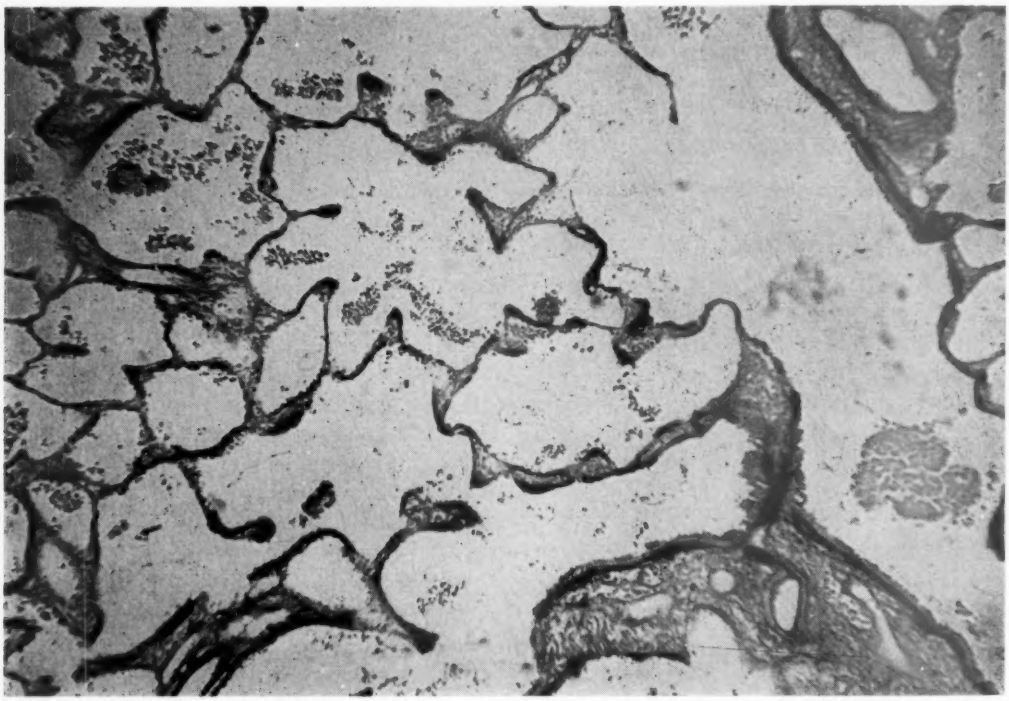

Fig. 1.—Case 3. Photomicrograph (×80; ¼ off reduction). Example of hypertrophic emphysema with alveolar distention and bleb formation (see text).

Case 3.—K. S., a white male infant, was born on May 10, 1956, following an uneventful full-term pregnancy and normal delivery. The baby breathed spontaneously and no resuscitation was necessary. Four weeks later respiratory difficulty was noted for the first time. Cyanosis and wheeze were not observed.

Because of the continued respiratory distress the infant was admitted to Buffalo Children's Hospital on July 17, 1956. On admission he was moderately dyspneic with respirations of 48 per minute, and a pulse rate of 110 per minute. Cyanosis was not observed. Costal retraction was noted with inspiration. Breath sounds were decreased over the right hemithorax. A systolic bruit was heard over the left parasternal area. The electrocardiogram showed suggestive right ventricular hypertrophy. The other laboratory findings were

noncontributory. Chest x-ray, however, showed increased radiolucency of the entire right hemithorax except for a small area of compressed lung at the apex corresponding to the right upper lobe. The mediastinum was only moderately shifted to the left. The infant appeared to improve slightly with oxygen. He was irritable and ate poorly. Bronchoscopy was negative. Because the clinical picture and x-ray findings remained unchanged, thoracotomy was performed on Aug. 3, 1956. The right middle lobe was found to be greatly distended, compressing the remaining lung parenchyma. No cause for the localized emphysema could be found. The lobe was easily resected and the remaining lung readily expanded to fill the hemithorax. On gross inspection, the lobe was pale pink in color and involved with diffuse emphysema. Microscopically the characteristic picture of hypertrophic pulmonary emphysema was seen without evidence of infection (Fig. 1). The lobar bronchus was normal.

The postoperative course was uneventful and when last seen in May, 1957, the child was asymptomatic with no further respiratory symptoms. The heart murmur persisted unchanged.

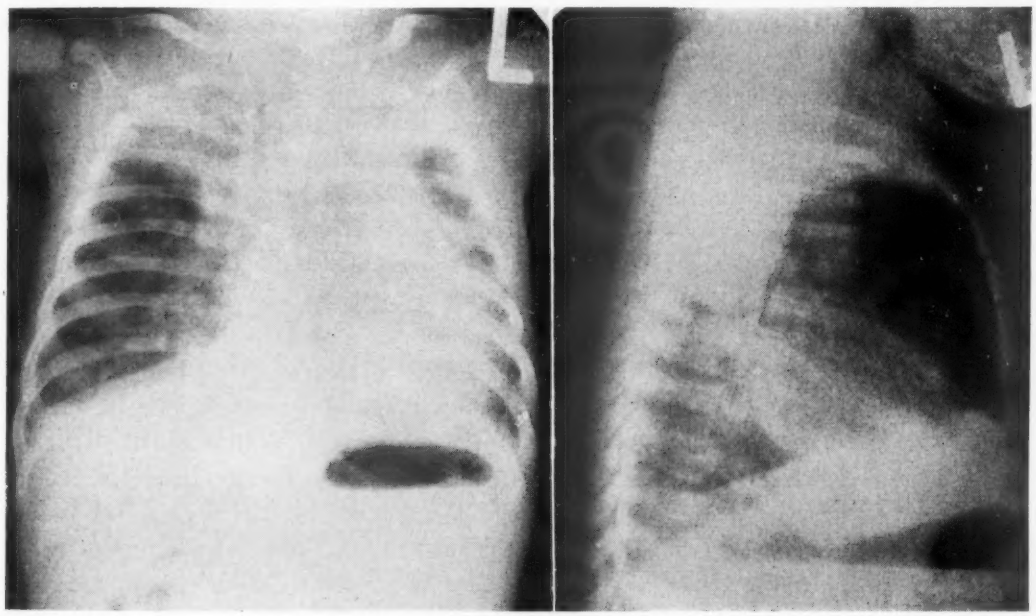

Fig. 2.—Case 4. Emphysema of right middle lobe (see text). Frontal and lateral x-ray films showing shift of mediastinum and compression of remaining lung parenchyma. Note herniation of lung seen best on lateral film.

CASE 4.—R. C., a white female infant, was born on May 15, 1956, after an uneventful full-term pregnancy. Delivery was by cesarean section following which resuscitation was said to have been necessary. Heavy breathing and cough were present since the time of birth. During the ensuing weeks the parents noticed one episode of questionable cyanosis. The infant did not eat well and gained weight poorly.

She was admitted to another hospital on Sept. 4, 1956, because of progressive dyspnea and transferred to Buffalo Children's Hospital one week later for further treatment. She was poorly nourished and dyspneic with a pulse rate of 160 per minute and respirations of 60 per minute. Decreased breath sounds and an increased percussion note were found over the right hemithorax. No wheeze was heard. A grade III systolic bruit was audible over the left precordium. There was no cyanosis. Laboratory work was noncontributory except for electrocardiographic evidence of combined ventricular hypertrophy. Chest x-ray showed shift of the mediastinum to the left and compression of the right upper lobe (Fig. 2). The patient was treated with oxygen and antibiotics but failed to improve. Because

of continued dyspnea a thoracotomy was performed on Oct. 4, 1956. The right middle lobe was markedly emphysematous, filling most of the right hemithorax. After it was removed the compressed upper and lower lobes expanded to fill the thoracic cavity. No cause for the emphysema was found at surgery. The resected lobe did not deflate. The bronchus appeared to be normal on gross and microscopic examination. The parenchyma showed the typical findings of hypertrophic pulmonary emphysema without evidence of infection. Scattered bleb formation was noted.

The patient was discharged after an uneventful postoperative course. She was readmitted to Buffalo Children's Hospital on Dec. 10, 1956, because of the persistent grade III systolic murmur. A patent ductus was diagnosed by cardiac catheterization. The ductus was ligated on Dec. 14, 1956, and she was discharged in excellent condition. When last seen in June, 1957, she was asymptomatic. No heart murmur was heard.

CLINICAL ANALYSIS

Nothing of significance was noted in the prenatal or birth history of the 40 cases reviewed. Premature births occurred in 4 per cent of the infants with localized pulmonary emphysema. This figure is not remarkable since it falls within the normal incidence of prematurity seen in an average large obstetrical service. Ehrenhaft[3] has suggested that vigorous resuscitation of the newborn might be a factor in the genesis of this condition. Of the 40 cases reviewed by us, 17 had no comment concerning resuscitation. In the remaining ones 22 per cent were definitely stated to have undergone resuscitative measures. Although this figure is higher than one might normally expect, it is difficult to evaluate since there were no detailed descriptions as to the nature and extent of the measures employed.

The sex incidence was significant in that the ratio of male to female infants was 2 to 1. In our group there were 3 males and 1 female. In the literature there were 21 male infants, 11 females, and 4 whose sex was not mentioned.

The predominant symptoms were those associated with progressive respiratory embarrassment. Dyspnea was mentioned in 33 of the 40 cases. Twenty-five infants were noted to have had cyanosis which was often intermittent. In 14 cases a wheeze had been heard. Feeding difficulty and cough were described in 9 and 8 cases, respectively. Only 6 infants had respiratory infections, and these were generally mild and appeared to have had no direct relationship to the emphysematous process. The average time of onset of symptoms was at the age of 25 days. In 17 infants symptoms began during the first week of life. In the remaining ones respiratory difficulty became apparent by 2 months of age except for 3 in whom the symptoms began between the second and sixth months.

The usual physical findings were those of respiratory distress; the severity was related directly to the degree of emphysematous lobar distention. The physical sign noted most frequently was mediastinal shift. In our experience the location of the apical heartbeat was the most reliable method for determining the degree of mediastinal deviation in infants. Inspiratory retraction, decreased breath sounds, and hyperresonance over the involved side of the chest were mentioned in slightly less than half of the 40 cases. Cyanosis and dyspnea were stated to be present in approximately one-third of the cases. In many

of the others continuous oxygen administration may have masked these signs. Interestingly enough, only 8 infants were noted to have wheeze during hospital admission.

Routine laboratory work including complete blood count and nasopharyngeal cultures were of no diagnostic significance. Roentgenographic studies, however, were most important in the diagnosis of this condition. The typical findings included mediastinal shift with mediastinal herniation in the more severe cases. The herniation was detected best on the lateral chest x-ray as an abnormally radiolucent area behind the upper sternum (Fig. 2). The emphysematous lobe frequently occupied the entire hemithorax. The diaphragm on the involved side was often depressed. Bronchography was generally of very little diagnostic value and could be dangerous in infants in respiratory distress.

Certain intrathoracic conditions must be considered in the differential diagnosis of localized pulmonary emphysema. The entities most commonly entertained are congenital lung cyst, pneumatocele, emphysema either obstructive or compensatory in nature, pneumothorax, and diaphragmatic hernia. A congenital lung cyst is often well outlined, spherical, and frequently surrounded in its entirety by normal or partially compressed lung parenchyma. Congenital cysts when multiple or fluid-containing present less of a problem in the differential diagnosis. Infectious pneumatoceles, particularly those seen with staphylococcal pneumonitis, may resemble a cystic or emphysematous area of lung. Pneumatoceles, however, are usually associated with pneumonitis both clinically and by x-ray and show a prompt response to antibiotic therapy. Localized obstructive emphysema is apparent by roentgen study, but its cause may remain obscure. Diagnostic bronchoscopy is often necessary to recognize a nonopaque foreign body or inspissated secretions. Agenesis of an entire lung with compensatory emphysema may resemble localized pulmonary emphysema on chest x-ray. Spontaneous pneumothorax may be confused with localized pulmonary emphysema. Careful examination of the chest roentgenogram will usually reveal the lung to be more or less symmetrically collapsed with a distinct border between it and the clear peripheral pneumothorax. Diaphragmatic hernia with intrathoracic stomach or intestine should seldom be confused with localized pulmonary emphysema on x-ray. The insertion of a nasogastric tube with the occasional addition of a radiopaque liquid may help to establish the diagnosis.

In most instances a detailed history and thorough physical examination with a frontal and lateral chest x-ray will permit a correct diagnosis of localized pulmonary emphysema. Needle aspiration or insertion of an intercostal tube has been performed to relieve the intrathoracic air tension. It is our feeling that unless one is certain of a diagnosis of pneumothorax these procedures are fraught with considerable danger. In the cases reviewed in which localized pulmonary emphysema was treated by needle aspiration or insertion of an intercostal tube, the results were uniformly bad leading to rapid deterioration and often death.

Bronchoscopy may be performed as a definitive procedure or just prior to thoracotomy. By direct inspection of the bronchial tree, obstruction due to

foreign body or inspissated secretions may be recognized and treated. Stenosis of a major bronchus due to external compression may be observed at bronchoscopy. Agenesis of the lung also may be recognized by bronchoscopic inspection.

Bronchoscopy is a relatively safe procedure in infants when performed by an experienced operator. The small size of the tracheobronchial tree may occasionally make thorough examination in the dyspneic infant less than the ideal achieved in a quiet adult. The normal tendency for the bronchi to narrow with expiration may appear exaggerated in the infant whose bronchi are naturally smaller and less firmly supported than those of the adult. With labored respirations the tendency toward expiratory collapse may become exaggerated. This was rather commonly observed in the cases that were bronchoscoped, but it was of little significance in establishing a specific cause of the localized pulmonary emphysema. It was not possible to demonstrate lobar bronchial collapse of a ball-valve type at bronchoscopy. Approximately one-third of the 40 cases reviewed in this study were bronchoscoped with results that were inconclusive.

TREATMENT

Progressive localized pulmonary emphysema is best treated by excisional surgery. Any patient suspected of having this disease with unimproved or progressive respiratory distress should have thoracotomy and excision of the emphysematous lobe. Occasionally thoracotomy may be necessary to establish the correct diagnosis. Thirty-five of the 40 infants had definitive pulmonary resection. The age at the time of surgery varied from 6 weeks to 4 years, with more than three-fourths of the patients under 6 months of age. The average age at the time of operation was 6.3 months. In more than half the cases the operation would seem to have been elective in nature and to have been performed because of persistent or slowly progressive symptoms. Ten other infants were operated upon as urgent respiratory problems meaning that the operation was necessary within several days after admission to the hospital due to progressive respiratory distress. Three cases were operated upon as emergency procedures within several hours after hospital admission because of their critical respiratory status.

The period between the onset of the anesthesia and the time the chest is opened may be critical. During this time the anesthetist may distend further the emphysematous lobe by forceful positive pressure through the endotracheal tube. The thoracotomy should be performed as rapidly as possible and the anesthetist should use no positive pressure until the chest has been opened. Upon opening the pleura the emphysematous lobe usually bulges out of the wound and allows the remaining normal lung to expand. The diseased lobe does not deflate and compresses the remaining lung when it lies in the hemithorax. Only rarely may the surgeon be able to demonstrate a cause for the localized emphysema. Excision of the diseased lobe is easily accomplished as

the hilar structures are free from inflammatory reaction. Following removal of the emphysematous lobe the remaining lung usually expands well to completely fill the pleural space. The postoperative course in all of our patients and most of those in the literature was essentially uneventful.

PATHOLOGY

Of the 35 cases undergoing excisional lung surgery there were 13 left upper lobectomies with 2 additional segmental resections of portions of the left upper lobe, 13 right middle lobectomies, and 7 right upper lobectomies. On gross inspection the typical resected specimen was a uniformly distended, smooth, pale, pink lobe with occasional subpleural emphysematous blebs. The lobe characteristically floated on water and did not deflate even when allowed to stand with the transected bronchus open. On cut section the lung tissue had a spongy appearance with numerous dilated alveoli. The localized emphysema was limited to either upper or middle lobe and for reasons not entirely clear the lower lobes were not involved in the disease process. Microscopic examination revealed distended alveoli, typical of hypertrophic pulmonary emphysema. The thin alveolar walls were irregularly ruptured to form blebs of various sizes (Fig. 1). Inflammation was notably absent. Careful examination of our surgical specimens* including special stains for elastic tissue revealed no abnormalities of the lobar bronchi.

The clinical and pathologic features of this disease are related to the extent of hypertrophic emphysema. The ball-valve type of obstruction to the lobar bronchus results in progressive alveolar distention and rupture. The involved lobe becomes progressively distended resulting in a shift of the mediastinum, compression of remaining normal lung tissue, and eventually cardiorespiratory decompensation. Despite careful gross and histologic examination of the lobar bronchus and lung parenchyma, there is often no evidence of bronchial obstruction. A number of causes for the disease have been mentioned in the literature, but the etiology still remains unsettled. The most commonly mentioned factor is hypoplasia or actual absence of the lobar bronchial cartilage. This abnormality was described in 11 of the 36 cases reviewed in the literature. In some cases, however, this conclusion appeared to be based upon the surgeon's impression rather than detailed histologic study. Careful examination of the 4 resected lobes from the Buffalo Children's Hospital revealed the cartilage in the lobar bronchus to be normal. Hypertrophic mucosa giving rise to mucosal valves was mentioned as the etiologic factor in 3 cases in the literature; this was not observed in our 4 specimens. Three other infants were found to have bronchial compression by external pressure due to a patent ductus, ligmentum arteriosum, or an anomalous vein. In all the remaining cases no mention was made of a specific etiologic agent. Demonstration of a ball-valve type of lobar bronchial obstruction will probably have to await special studies in the living subject.

*All sugrical specimens were examined by Dr. Kornel Terplan, Pathologist, at the Buffalo Children's Hospital.

RESULTS

Four of the 5 patients not treated by pulmonary resection had either needle aspiration or closed intercostal tube drainage of the emphysematous lobe and all so treated died. The fifth infant in this group was treated expectantly and also died. In the 35 patients treated by pulmonary resection there were 2 deaths. One expired approximately 12 hours postoperatively with an overwhelming pneumonia in the remaining lung. The second death occurred one month after surgery from progressive emphysema. Twenty-six of the 33 remaining surgical cases were asymptomatic at the time of their last examination. This included the 4 new cases reported in this paper which have been followed from 1 to 8 years after surgery. Three of the remaining 7 cases were noted to have one or more residual areas of emphysema; the other 4 cases were lost to follow-up.

SUMMARY

1. Four cases of localized pulmonary emphysema from the Buffalo Children's Hospital along with a total of 36 cases from the English literature are reviewed.

2. A correct diagnosis of this disease can usually be made from a careful history, physical examination, and roentgenogram of the chest.

3. Resection of the involved lobe leads to immediate improvement and cure in most cases. Temporizing measures are inadequate and may prove to be fatal.

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EFFECT OF SUTURE MATERIAL ON URINARY BLADDER WOUND HEALING

Experimental Study

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CATGUT is established as the best suture material to be employed in the repair of wounds of the urinary tract. The basis for its success is an extensive and impressive clinical experience and the frequent adverse reports found in the literature when unabsorbable suture material was employed.[1]

Since a review of the literature failed to yield experimental confirmation of these clinical observations, the following work was undertaken.

METHODS

Thirty-seven adult mongrel dogs of both sexes, weighing between 8 and 10 Kg., were used. Under pentobarbital anesthesia the urinary bladder was exposed aseptically and 2 parallel incisions about 2 cm. each were made on its ventral surface. The incisions were then sutured by the following techniques: (a) a continuous suture including all coats and everting the wound edges and (b) a continuous suture excluding the bladder mucosa. Finally, different types of suture material were used for the different series of experiments. These were (a) 5-0 chromic catgut, (b) 5-0 silk, (c) stainless steel single thread 6-0 wire, and (d) commercial grade cotton No. 40. The dogs were returned to the cages following the operation and given the usual care but excluding antibiotics. The period of observation lasted till they died or were sacrificed.

RESULTS

Five dogs died in the postoperative period and 32 were sacrificed, at intervals ranging from 9 to 70 days after the day of operation. The average postoperative time when sacrificed was 3 weeks.

Table I shows the results in 8 dogs on which the bladder incisions were closed with a continuous suture excluding the mucosa. One incision was sutured with chromic catgut and its mate with 5-0 silk. All the catgut suture lines healed per primum but 2 showed some inflammatory reaction. When silk was employed the following complications occurred; one developed a urinary fistula, another had a urinary stone at the suture, and, although 5 showed moderate inflammation, 7 healed per primum.

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TABLE I. CONTINUOUS SUTURE EXCLUDING MUCOSA (8 DOGS)

SUTURE MATERIAL	FISTULA	CALCULUS	INFLAMMATION	PER PRIMUM
Chromic catgut	0	0	2	8
Silk	1	1	7	7

Six dogs were used in the series summarized in Table II and the incisions were sutured with a continuous suture including all layers of the bladder wall with either catgut or silk. The chromic suture line showed 2 instances of fistula formation and 5 had inflammatory reactions. On the silk suture there was one calculus formed and 5 inflammatory reactions but no fistulas were found.

TABLE II. CONTINUOUS SUTURE INCLUDING ALL COATS (6 DOGS)

SUTURE MATERIAL	FISTULA	CALCULUS	INFLAMMATION	PER PRIMUM
Chromic catgut	2	0	5	4
Silk	0	1	5	6

In a series of 5 dogs (Table III) continuous sutures including all coats of the bladder were employed and were repaired with either chromic catgut or stainless steel wire. The chromic catgut sutures yielded 2 fistulas. There was one inflammatory reaction and 3 healed per primum. The stainless steel side presented one instance of fistula and one of calculus formation with 4 wounds healing by first intention.

TABLE III. CONTINUOUS SUTURE INCLUDING ALL COATS (5 DOGS)

SUTURE MATERIAL	FISTULA	CALCULUS	INFLAMMATION	PER PRIMUM
Chromic catgut	2	0	1	3
Stainless steel	1	1	0	4

In 5 dogs (Table IV) mucosa-excluding sutures with silk and stainless steel were employed. On the silk line one showed an inflammatory reaction while on the stainless steel side there was one urinary stone observed. All these wounds healed per primum.

TABLE IV. CONTINUOUS SUTURE—MUCOSAL EXCLUSION (5 DOGS)

SUTURE MATERIAL	FISTULA	CALCULUS	INFLAMMATION	PER PRIMUM
Silk	0	0	1	5
Stainless steel	0	1	1	5

In the series of 5 dogs shown in Table V only commercial cotton was used as suture material. One incision was closed including the mucosa and the other excluding it. There were 3 instances of fistula formation, one on the side which excluded mucosa, and 2 where mucosa was included. Although no calculus was found, inflammation was observed in 7 of the 10 incisions.

TABLE V. CONTINUOUS COTTON SUTURE (5 DOGS)

SUTURE MATERIAL	FISTULA	CALCULUS	INFLAMMATION	PER PRIMUM
Excluding mucosa	1	0	3	4
Including mucosa	2	0	4	3

DISCUSSION

The experiments in this study are best summarized in Tables VI, VII, and VIII.

TABLE VI. CONTINUOUS SUTURE INCLUDING ALL COATS

SUTURE MATERIAL	NUMBER OF DOGS	FISTULA	CALCULUS	INFLAMMATION	PER PRIMUM
Chromic catgut	13	4	0	7	9
Silk	8	0	1	6	8
Stainless steel	7	1	2	1	6
Cotton	7	2	0	5	5

TABLE VII. MUCOSA-EXCLUDING CONTINUOUS SUTURE

SUTURE MATERIAL	NUMBER OF DOGS	FISTULA	CALCULUS	INFLAMMATION	PER PRIMUM
Chromic catgut	10	0	0	2	10
Silk	15	1	1	8	14
Stainless steel	7	0	1	1	7
Cotton	7	1	0	3	6

TABLE VIII. COMPARISON OF TYPE OF SUTURE AND MATERIAL

SUTURE MATERIAL	TYPE OF SUTURE	NUMBER OF DOGS	FISTULA	CALCULUS	INFLAM-MATION	PER PRIMUM
Chromic catgut	Mucosal exclusion	10	0	0	2	10
	Mucosal inclusion	13	4	0	7	9
Silk	Mucosal exclusion	15	1	1	8	14
	Mucosal inclusion	8	0	1	6	8
Stainless steel	Mucosal exclusion	7	0	1	1	7
	Mucosal inclusion	7	1	2	1	6
Cotton	Mucosal exclusion	7	1	0	3	6
	Mucosal inclusion	7	2	0	5	5

Where the mucosa was included in the suture, fistula formation was observed in 7 of 35 experiments. Thus 1 of 5 dogs developed a fistula and 2 others developed urinary stones on the suture. Although 28 of these wounds healed per primum, 17 showed a moderate degree of inflammatory changes; thus in only 11 instances did a good uneventful healing occur.

The mucosa was excluded in 39 preparations and in only 2 occasions fistulas were produced. Both occurred in dogs with an unabsorbable suture line. Two calculi were noticed in the whole series, again where unabsorbable suture material had been used. Although 14 suture lines had a moderate degree of inflammation, 37 had healed per primum. Catgut suture lines where the mucosa was excluded healed better than all others.

A comparison of the same suture employed in different fashions is depicted in the last table. The advantages of a suture which excluded the mucosa over

one that is all inclusive is clearly demonstrated. It seems that an absorbable suture is likewise advantageous.

SUMMARY

1. An experimental study on the effect of suture materials and types of suture on urinary bladder healing has been presented.

2. The clinical experience on the superiority of absorbable suture seems to be sustantiated by this study.

3. Mucosal suturing is of importance in the development of complications, and when excluded healing occurred by first intention.

4. This is a preliminary report on this subject that is under further investigation.

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THE INTERACTION OF PAPAIN, UREA, AND WATER-SOLUBLE CHLOROPHYLL IN A PROTEOLYTIC OINTMENT FOR INFECTED WOUNDS

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IN RECENT years there has been a marked increase in interest in the idea of using proteolytic enzymes in the local treatment of infected wounds. This concept has a logical basis, for theoretically these enzymes should be ideal agents for producing clean healing wounds.

In actual practice the proteolytic preparations which have been used locally have limiting characteristics which have prevented their use on as broad a scale as it is desired practically. Débridement has been too slow as compared to the action which might be obtained from the ideal enzyme. In addition, physicians have been reluctant to employ therapy with an enzyme unless an experienced person could be in attendance. Moreover, the proteolytic preparations currently available must be prepared freshly at the time of use and must be used fairly promptly since they have a relatively short half-life. These factors have confined the use of the proteolytic enzymes in this way largely to hospitals and institutions in which adequate facilities for manipulation of the preparations and ample supervision of their use were available.

More recently a proteolytic ointment which appears to eliminate to a considerable degree the disadvantages of the proteolytic agents in current use has been employed. Because this preparation represented a marked departure in formulation from other proteolytic enzymes which are used locally and because the clinical results were uniformly excellent,[11] a detailed report of the actions of this proteolytic ointment is being made.

The proteolytic ointment contains 10 per cent papain, 10 per cent urea, and 0.5 per cent water-soluble chlorophyll as its active ingredients. In actual usage it is stable indefinitely on storage, uniformly active when applied to wounds, and virtually without untoward effects even when allowed to remain in the wound for prolonged periods of time.

There are several apparent contradictions in the action of this preparation if the literature on papain is studied. Hwang and Ivy[9] have reviewed this literature very thoroughly. Papain, an enzyme with a broad spectrum of activity, is derived from the carica papaya. The enzyme has a rather extensive background of clinical usage.

In a solution or in the presence of moisture, papain is reported to lose its activity rather rapidly. This is at variance with the retention of activity by the enzyme for indefinite periods in the preparation at hand. In solution

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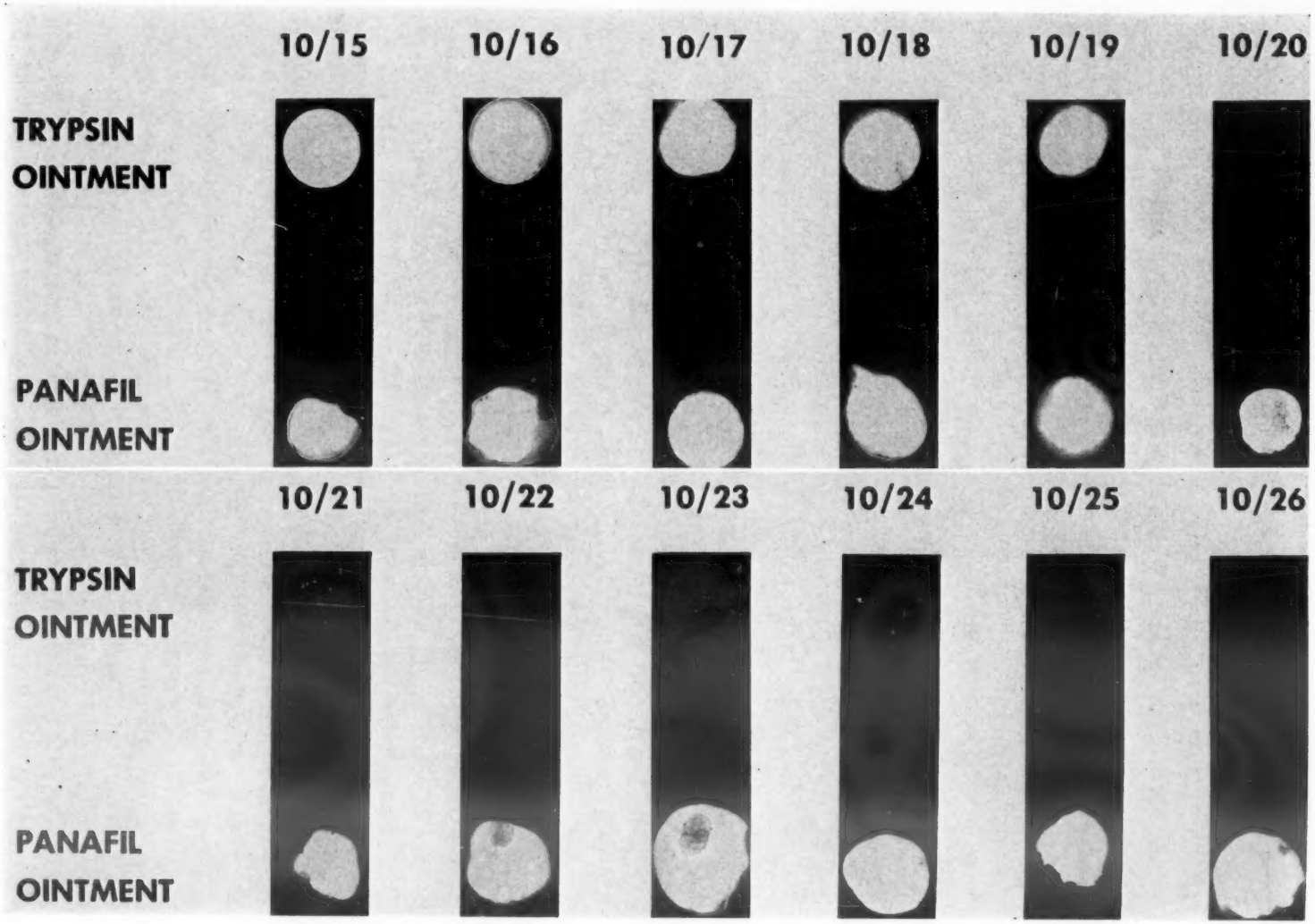

Fig. 1.—Stabilities of trypsin ointment and Panafil ointment.

papain does lose activity significantly over the first 24 to 48 hours, but, subsequently, the activity is rebuilt to original levels or in some cases higher. For example, a 10 per cent solution of papain in distilled water was assayed for papain activity by the method of Blau[3] immediately after preparation and at later intervals. The Blau milk-clotting units per milliliter of the solution were 96.0 initially, 73.5 at 24 hours, and 125.0 at the end of 38 days. Although this phenomenon occurs uniformly, an explanation for the observation has not been found. It seems possible, however, that previous reports of the instability of papain in solution may have been based upon tests of short duration and that investigations over longer periods of time would have demonstrated the rebuilding of the activity of the papain.

The same phenomenon has been observed with the ointment preparation used clinically. After a loss of activity in the first 24 hours, the activity of the papain of this preparation rebuilds to original levels or higher and remains at the high level indefinitely. Two typical batches of ointment assayed at intervals had the following Blau milk-clotting units per milliliter of ointment: (a) 57.6 initially, 47.0 at 3 days, 56.7 at 22 days, and 59.5 at 403 days, (b) 62.7 initially, 56.7 at 19 days, and 58.4 at 400 days.

Papain, in contrast to trypsin, for example, requires the presence of an activator to exert its digestive function. The sulfhydryl groups furnish the exogenous activation which papain requires. It is understandable, therefore, that papain in sterile solution, which does not contain an activator, might be stable indefinitely. Since trypsin does not require exogenous activation, it is likewise rational to accept as fact that this enzyme soon loses its activity in the presence of moisture. This point is demonstrated in Fig. 1 which illustrates a test in which a trypsin ointment, which was freshly prepared from the crystalline enzyme, was used to digest the emulsion of gelatin on a photographic film. When it was freshly made, the ointment readily digested the emulsion within 30 minutes. The preparation retained sufficient activity through the subsequent 4 days to complete digestion in 30 minutes. Thereafter remaining activity was too small to digest the emulsion completely. In contrast is the Panafil ointment containing papain, urea, and chlorophyll which was tested simultaneously. This ointment, 8 months old at the time of the test, was as active on the eleventh day, when the test was stopped, as it had been on the first day.

Neither urea nor water-soluble chlorophyll contain groups which could activate papain so that their presence would not affect stability. The question remained, though, as to how or whether papain found activation when applied to wounds. Preliminary clinical studies showed that papain alone did not uniformly find activators in the wounds to which it was applied. In some wounds the unactivated enzyme produced digestion. In others it was totally lacking in activity. When urea was added to the papain, the enzyme was uniformly active in the wounds. It was concluded that the urea acted upon the protein substrates of the debris in the wound to expose radicals which caused activation of the papain. Some knowledge of the nature of urea is required to understand its action in this regard.

Urea is an excellent denaturant of certain proteins, attacking them without respect to type and without entering into chemical combination with them. Cystine is apparently the key link in the polypeptide structure at which urea acts.[4-8, 13-15] Cystine exists in straight and cyclic forms in proteins. Little change in the molecular mass of proteins occurs when the cystine is in a terminal position or near one, but marked changes are effected when this amino acid is in a more central position. Sulfhydryl groups appear in such solutions. The cyclic form resists attack by urea. Only disulfide groups are found in these solutions. Since sulfhydryl groups activate papain, it is understandable that the action of the urea on a susceptible protein substrate should insure digestive activity of the papain.

The utility of urea in combination with papain goes beyond its activating function. Numerous proteins in their native state are highly resistant to enzymatic digestion. Such proteins, with few exceptions, however, become susceptible to digestion when acted upon by a denaturant with fission of the complex protein structure. Urea, which is an effective denaturant and protein solvent, thus prepares the protein substrate for more rapid and complete proteolytic activity. This fact was demonstrated in an experiment of which the details are tabulated in Table I. Using Difco beef powder as the substrate, the digestive ability of crystalline papain was assayed at 37° C. for 2 hours, alone and in combination with increasing amounts of urea. A significant increase in the quantity of beef powder digested was noted when urea was combined with crystalline papain. Digestive ability increased with increased molarity of the urea up to a concentration of 6 molar.

TABLE I. DIGESTION OF BEEF POWDER BY CRYSTALLINE PAPAIN ALONE AND IN COMBINATION WITH INCREASING AMOUNTS OF UREA

ACTIVE INGREDIENTS	VOLUME OF BEEF POWDER REMAINING AFTER DIGESTION FOR 2 HOURS AT 37° C. (ML.)	WEIGHT OF BEEF POWDER REMAINING AFTER DIGESTION FOR 2 HOURS AT 37° C. (GM.)
None	3.2	0.66
Urea, 2 molar	3.4	0.68
Urea, 4 molar	3.9	0.63
Urea, 6 molar	5.0	0.61
Crystalline papain, 10 mg.	2.3	0.39
Crystalline papain, 10 mg., and urea, 2 molar	2.6	0.34
Crystalline papain, 10 mg., and urea, 4 molar	2.3	0.265
Crystalline papain, 10 mg., and urea, 6 molar	2.3	0.195

It was of interest to define the fact that the effect of urea was upon the protein substrate rather than upon the papain. This was done by employing a substrate already denatured, upon which urea could not be expected to have further effect. Egg albumin heated at 70° C. for 20 minutes to produce denaturation was employed as the substrate for this purpose. The addition of urea did not enhance the digestive ability of commercial papain under these circumstances (Table II). If anything, urea may have in this case slightly decreased the digestive activity.

TABLE II. DIGESTION OF DENATURED ALBUMIN

ACTIVE INGREDIENTS	WEIGHT IN GRAMS REMAINING AFTER DIGESTION FOR 2 HOURS AT 37° C.
None	0.995
Commercial papain, 10 mg.	0.71
Commercial papain, 10 mg., and urea, 3.0 Gm.	0.83
Commercial papain, 10 mg., and water-soluble chlorophyll, 10 mg.	0.79
Varidase, consisting of streptokinase, 10,000 units, and streptodornase, 2,500 units	0.92
Varidase, consisting of streptokinase, 10,000 units, and streptodornase, 5,000 units, and human blood serum, 2.0 ml.	1.0
Varidase, consisting of streptokinase, 20,000 units, and streptodornase, 5,000 units, and human blood serum, 2.0 ml.	0.95
Proteinase A, 15,000 units	0.69
Trypsin, 2.5 mg.	0.84
Trypsin, 2.5 mg., and urea, 3.0 Gm.	0.95

Of interest are several other items which appear in Table II. Water-soluble chlorophyll was combined with commercial papain without effect on digestive ability. Comparative values for commercial papain and other available proteolytics were also obtained. Commercial papain and Proteinase A were about equal in digestive efficacy with this substrate. Varidase, which is composed of streptokinase and streptodornase, was relatively without effect in this test. It can be seen that, when urea was added to trypsin, the enzyme lost digestive ability. This effect of urea has previously been noted by Viswanatha and Liener.[19]

Table III summarizes tests of the effect of commercial papain on an undenatured substrate which urea does not affect. Casein is suitable for this purpose. It has a very low cystine content and the cystine is in a terminal position in the molecule. The urea did not increase digestion in this case, but the commercial papain was active without the addition of an activator. It is inferred from this experiment that when cystine is in a terminal position in the protein

TABLE III. DIGESTION OF CASEIN

ACTIVE INGREDIENTS	0.1 N NaOH (ML.) REQUIRED TO NEUTRALIZE ACID GROUPS EXPOSED BY DIGESTION FOR 2 HOURS AT 37° C.	DIGESTION ATTRIBUTABLE TO ACTIVE INGREDIENTS IN ML. OF 0.1 N NaOH
None	26.05	—
Commercial papain, 0.5 Gm.	55.8	29.75
Commercial papain, 0.5 Gm., and urea, 0.5 Gm.	56.8	30.75
Commercial papain, 0.5 Gm., and water-soluble chlorophyll, 0.025 Gm.	56.0	29.95
Commercial papain, 0.5 Gm., urea, 0.5 Gm., and water-soluble chlorophyll, 0.25 Gm.	55.5	29.45
Varidase, consisting of streptokinase, 10,000 units, and streptodornase, 5,000 units, and human whole blood, 1.0 ml.	30.1	4.05
Trypsin, 0.005 Gm.	31.5	5.45

molecule, the sulfhydryl groups required for activation are available to commercial papain. Thus in this instance where urea is ineffective, its effect is not required. In this test again, the water-soluble chlorophyll was included and found to be without effect upon the activity of the commercial papain.

Neuman and Tytell[16] reported that denaturation of collagen by urea resulted in increased digestion by papain. A combination of crystalline papain and urea did not produce this result in the present investigation (Table IV). Effective digestion of collagen was obtained only by the enzyme derived from the *Clostridium histolyticum* (Lederle). It is true that urea affected collagen as can be seen from the increased volumes in the solutions of urea. This represents swelling produced by the denaturant. It did not, however, render collagen susceptible to digestion by crystalline papain.

TABLE IV. DIGESTION OF COLLAGEN

ACTIVE INGREDIENTS	VOLUME OF COLLAGEN IN ML. AFTER DIGESTION FOR 12 HOURS AT 37° C.
None	0.8
Enzyme of *Clostridium histolyticum* (Lederle), 10 mg.	0.325
Crystalline papain, 10 mg.	0.8
Crystalline papain, 10 mg., and urea, 3.6 Gm.	1.1

One of the useful effects produced by the proteolytic preparations in infected wounds is a marked reduction in the viscosity of pus which may be present. This effect is very noticeable with the streptodornase portion of Varidase. Therefore, the efficacy of the various enzymes in reducing the viscosity of an 0.05 per cent solution of desoxyribonucleoprotein was studied. Varidase was the most effective preparation employed (Table V). Crystalline papain alone produced a significant effect which was somewhat heightened by the addition of urea.

TABLE V. EFFECT OF VARIOUS ENZYMES UPON VISCOSITY OF A 0.05 PER CENT SOLUTION OF DESOXYRIBONUCLEOPROTEIN IN DISTILLED WATER

ACTIVE INGREDIENTS	VISCOSITY WITH DISTILLED WATER TAKEN AS 1.0	PER CENT REDUCTION IN VISCOSITY ATTRIBUTABLE TO ACTIVE INGREDIENTS
None	4.07	—
Crystalline papain, 0.5 Gm.	1.79	74.3
Urea, 0.5 Gm.	2.61	47.5
Crystalline papain, 0.5 Gm., and urea, 0.5 Gm.	1.63	79.8
Trypsin, 0.025 Gm.	3.41	21.4
Varidase, consisting of streptokinase, 100,000 units, and streptodornase, 25,000 units, and human blood serum, 2.5 ml.	1.33	89.0

Lipase activity has been reported for papain. An investigation of this point was carried out using the method of Willstätter, Waldschmitt-Leitz, and Memmen.[20] A lipase activity of 1.43 units was established, which is without marked significance.

Amylase activity was also investigated. It was not found to be present.

The reasons for including water-soluble chlorophyll in the preparation under study were of interest. While this agent has an excellent and voluminous clinical background, the necessity for its inclusion in a product designed primarily to remove wound debris may not seem readily apparent. This need becomes clearer on observing the clinical results with and without the water-soluble chlorophyll present in the combination. Preliminary clinical trials demonstrated that whereas the combination of commercial papain and urea without water-soluble chlorophyll provided rapid digestive activity, the ointment was likely to cause pain and irritation of the skin when allowed to remain in the wound for long periods. When water-soluble chlorophyll was added to the combination, these untoward effects were virtually eliminated. On several occasions when large amounts of wound debris have been digested, inflammation of the skin has resulted. In these cases it was assumed that the large amount of digested material overwhelmed the supply of water-soluble chlorophyll available. In each instance the frequency of the dressings was increased for a short period of time with disappearance of the inflammation. A return was then made to less frequent dressings with a continued absence of inflammation.

An attempt has been made to define the mechanism whereby water-soluble chlorophyll controls the irritation and inflammation which can be caused by proteolytic action in wounds. Commercial papain and the other proteolytic enzymes which are used clinically are not in themselves irritating or inflammatory and they are self-limiting in the sense that they attack only protein matter and are innocuous to viable tissue. It is therefore necessary to look at the products of the digestion produced by the enzyme to find the damaging substances which chlorophyll might be affecting.

Sack and Barnard[17] showed the presence of hemagglutinating substances in poorly healing wounds. Barnard[2] demonstrated that such hemagglutinating substances were capable of causing inflammation and necrosis. He also showed that water-soluble chlorophyll was a nonspecific inhibitor of the activity of these substances. It is entirely within the realm of possibility, and a concept of great importance if it is true, that split protein end products cause agglutination of red blood cells in the smaller blood vessels surrounding an area of infection and lead to localized necrosis. The demonstration of Barnard[2] that the IV-6 globulin fraction of human plasma possesses the ability to cause agglutination of red blood cells of group O Rh negative human blood and his finding that dilute solutions of water-soluble chlorophyll inhibit such agglutination has been confirmed (Figs. 2 and 3).

It has been demonstrated previously that water-soluble chlorophyll is able to unite with fibrinogen in apparently stoichiometric amounts to prevent fibrin formation on addition of thrombin.[1] This action of water-soluble chlorophyll has been confirmed.[12] The prevention of the formation of fibrin in an infected wound initiates many changes which lead to healing in the wound.

It has been found that blood proteins adsorb water-soluble chlorophyll.[18] Solutions of albumin removed significant amounts of chlorophyll from solution.

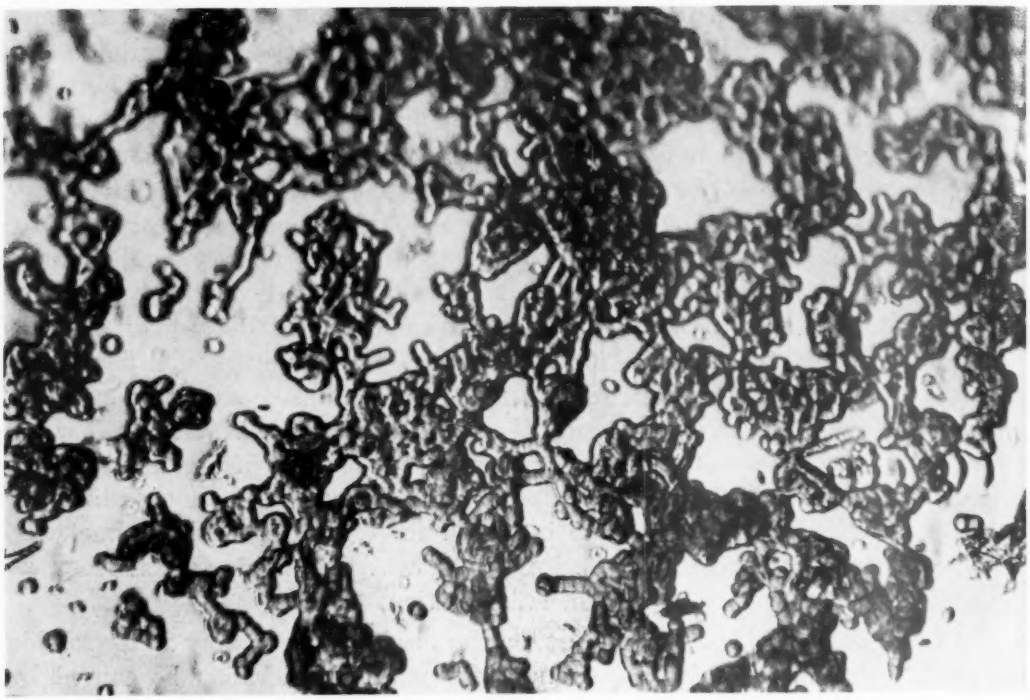

Fig. 2.—Agglutination of red blood cells of group O Rh negative human blood by the IV-6 globulin fraction of human blood plasma.

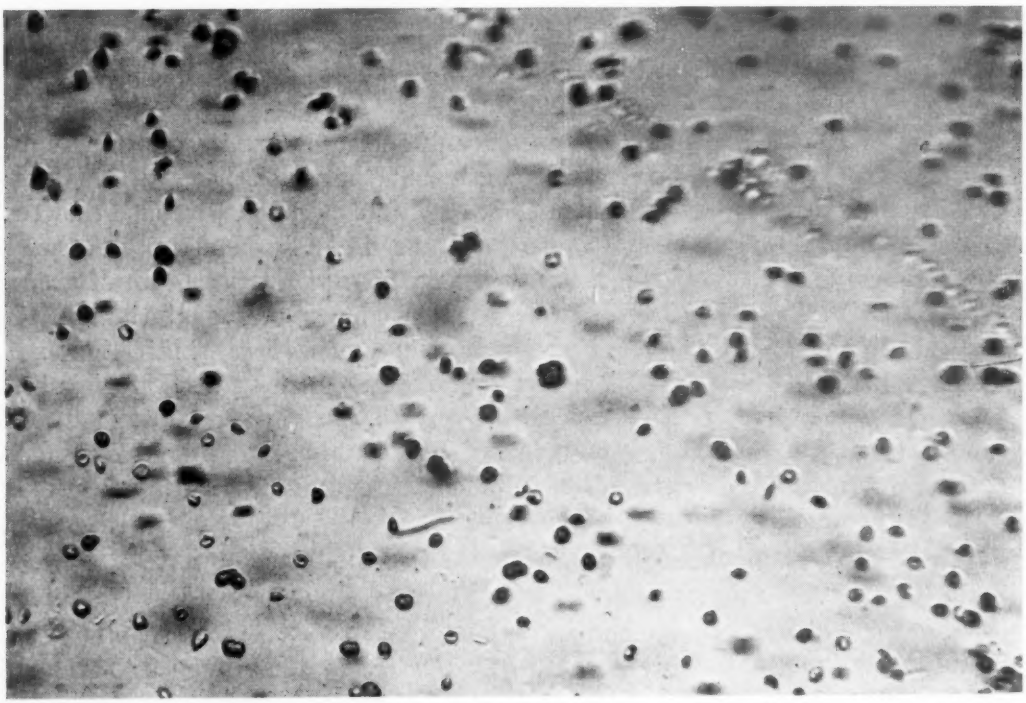

Fig. 3.—Inhibition of the water-soluble derivatives of chlorophyll of agglutination of red blood cells of group O Rh negative human blood by the IV-6 globulin fraction of human blood plasma.

This point is corroborated also by the combination of fibrinogen and water-soluble chlorophyll.[1, 12] Studies have also shown that the sedimentation rate of human red cells is decreased by water-soluble chlorophyll as would be expected in the light of the data on fibrinogen.[10]

These divers in vitro effects of water-soluble chlorophyll are interrelated in that the mechanism in each case appears to be a stoichiochemical combination with, or competitive inhibition of, protein substances. Likewise in the infected wound, water-soluble chlorophyll seems to complement proteolytic action by its control of the damaging aspects, direct or indirect, of certain proteins. The antihemagglutinative activity of water-soluble chlorophyll and its inhibition of fibrin formation may be the means by which this ingredient can help maintain patent blood and lymphatic vessels which in turn provide necessary humoral defenses, relieve edema, and remove the products of digestion from the wound. In addition, water-soluble chlorophyll may act by direct combination with the products of proteolytic digestion. These activities not only contribute to the safety of the proteolytic preparation, and hence its practical usefulness, but also help produce the conditions necessary for ultimate healing of the wound.

SUMMARY

The interaction of the active ingredients in a preparation containing commercial papain, urea, and water-soluble chlorophyll was studied. The enzymatic activity of commercial papain, the effect of urea upon the activity and the stability of commercial papain, and the action of water-soluble chlorophyll upon the activity of the combination of commercial papain and urea were evaluated. It is felt that the combination of commercial papain, urea, and water-soluble chlorophyll had advantages in regard to rapidity and completeness in removing wound debris, freedom from untoward side effects, stability, and convenience of use, which eliminated many of the practical limitations of the proteolytic agents which were available previously for the local treatment of infected wounds.

Thanks are given to Benjamin Goldman, A.B., who gave help in the laboratory in doing the experiments. Appreciation is extended for the provision of the enzymes indicated by the following pharmaceutical companies: crystalline papain and crystalline chymopapain—Winthrop Stearns, Incorporated, New York City; commercial papain—Rystan Company, Mount Vernon, N. Y.; Varidase and enzyme from the *Clostridium histolyticum*—Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.; Proteinase A—Sharp and Dohme, West Point, Pa., and trypsin—The National Drug Company, Philadelphia.

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OPERATIVE DECOMPRESSION OF CONSTRICTING BURNS

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THE management of constricting burns has received limited attention in the surgical literature. Nevertheless, such burns do present a problem which requires special consideration and we have found that our experiences with this entity have been shared by other surgeons concerned with the care of burned patients.

A recent circumferential deep burn of an extremity typifies the lesion. Infliction of the burn is followed by progressive signs and symptoms of vascular and neurologic impairment in the distal part of the limb. The burn is usually full thickness but may be partial thickness or mixed in depth. Frequently it is limited to a segment of a limb but the burn may involve an entire extremity. The distribution of the burn is influenced by the burning agent and the protective clothing worn at the time of the burn. These burns are produced by intense local heat applied by burning clothing or prolonged immersion in hot liquid or molten metal. While gloves and boots or shoes may protect distal parts from direct deep burn damage, the hand or foot of the involved limb may be seriously jeopardized by the constricting action of the proximal burn.

Clinically, as burn edema develops, progressive swelling of the distal part is noted. Moderate swelling and extreme tenseness of the deeply burned segment become apparent. The hand or foot assumes a cyanotic appearance as venous congestion progresses; this may be superseded by mottling. The arterial pulses are diminished or absent. The patient develops ischemic pain which may be accompanied by tingling and numbness. Movement of distal parts becomes increasingly difficult. Anesthesia, paralysis, and digital necrosis are early sequelae in cases of marked burn constriction.

PATHOGENESIS

The deep burn, involving most or all of the circumference of an extremity, acts as a rigid tourniquet on the underlying soft tissues. This inelastic encasement interferes with venous return causing congestion, increased capillary permeability, and an increase in extracellular fluid. When tissue tension is elevated sufficiently, impairment of arterial flow accounts for the syndrome of ischemia. Mechanical arterial compression is undoubtedly complemented by reflex vasospasm. In those cases where survival of the limb is not in doubt, local

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changes often lead to irreversible fibrosis of muscles resulting in disabling contractures. It is postulated that this course of events is responsible for permanent damage to burned limbs seemingly out of proportion to the effects expected from the depth and extent of the burns.

TREATMENT

Edema of the burned limb can be limited to some extent by elevation, immobilization, and application of a proper pressure dressing. These measures are most effective when initiated promptly after the injury. When this conservative program does not suffice to relieve excessive tissue tension underlying and distal to the burn, operative decompression should be instituted.

If the patient is admitted to the hospital within an hour or so of injury and doubt exists as to the necessity for decompression, it is advisable to wrap the involved part in sterile towels, elevate the limb, and observe the patient for several hours. When some time has elapsed between burning and admission to the hospital, the indications for decompression will be evident if they are going to appear.

Decompression may be accomplished by one or more incisions through the burn or by excision of the burned area. Certain cases lend themselves to a combination of these two methods, that is, initial incisional decompression followed by excision of the burn.

Incisional Decompression.—Decompression by incision(s) can usually be accomplished without general anesthesia. This is the method of choice in patients who are too ill to tolerate anesthesia and the trauma of excision because of serious pre-existent disease or extensive total body burns. When the circumferential burn is of deep partial thickness depth, decompression by incision(s) is used in preference to excision regardless of other conditions.

A single incision is made extending the length of the burn and carried down to deep fascia. It should be emphasized that simple "nicking" of the burn is not sufficient. Rarely, it is necessary to incise the deep fascia to effect decompression. If a single incision appears to be inadequate, one should not hesitate to use multiple incisions, placing them laterally to avoid exposure of important structures. Where the offending burn is of obvious full thickness depth, linear incisions are acceptable; in burns of incomplete dermal depth recognized lines of incision should be observed. Separate incisions on the dorsum of the hand or foot are indicated only when these distal parts are involved directly by the constricting burn.

Following decompression of the burn, rapid improvement in the color of the limb is noted; distal pulsations (where previously absent) return. The limb loses its tense appearance. The conscious patient notes a rapid disappearance of numbness although a short period of excruciating pain may be experienced with the sudden increase in blood flow. The patient's ability to move distal parts soon improves.

Patients with full thickness burns require no anesthesia for decompression. Basal sedation or light general anesthesia is used in cases in which the

constricting burn is of incomplete dermal depth. The procedure can be performed in the ward treatment room although operating room conditions are preferable. Hemorrhage following incision of the burn is not a serious problem; occasionally a vessel requires ligation.

Striking visual confirmation of the adequacy of decompression is given by the intravenous injection of the dye Disulphine Blue V. (Imperial Chemical Industries Medical Division). This test gives a picture of circulation in skin and soft tissues. Injecton of the dye before decompression shows poor concentration in the surface tissues distal to the constricting burn; in severe cases staining is virtually absent. Within a few minutes of decompression, dye enters the skin of the distal parts and the subcutaneous tissues of the burned area (as seen via the incision) become perfused with dye.

Following decompression an adequate pressure dressing is applied to the affected limb. The dressing is covered with a light plaster of Paris shell and the limb is elevated. Should doubt remain as to the circulation in the distal parts, the tips of the digits may be left exposed. The subsequent treatment of the burn will depend upon the general condition of the patient, the surface extent of the burn, and the preference of the surgeon. As a rule, we prefer to excise the areas of full thickness burn at the earliest opportunity rather than wait for the slough to separate.

Early Excision.—Immediate excision of the offending burn is the ideal method of decompression, particularly in patients with burns of limited extent and demarcated full thickness depth. In the operating room, excision of the entire burn, preferably down to deep fascia, is performed with the patient under general anesthesia. In most cases we prefer to delay skin grafting for one to 2 weeks, using an adequate pressure dressing to cover the extremity in the interim. This allows edema to subside and natural hemostasis to occur. At the second operation skin strips of intermediate thickness are taken with a free skin knife or a dermatome and applied to the granulating defect, natural flexion creases being observed. In certain elderly patients, to whom prolonged immobilization and/or recumbency is often fatal, it may be lifesaving to combine primary excision with immediate grafting.

In certain cases the 2 methods of decompression may be employed. Two specific situations warrant this combination. The constricting burn of the patient requiring resuscitation may be incised while salt and colloid solutions are being administered. Should the patient's condition become stable within a day or 2, excision of the burn may then be carried out. Limited constricting burns, of indeterminate depth, may be incised in the operating room with the patient anesthetized. With the involved tissues relieved of extreme tension, diagnosis of burn depth can be made with greater accuracy. Should a burn in this category be determined to be of full thickness depth following this procedure, excision can be performed at the same operation.

CASE REPORTS

CASE 1.—F. P., a 15-year-old painter, was using a blow torch when a spark exploded a can of gasoline nearby. His right sleeve caught fire and was extinguished by fellow

workmen. He was brought directly to our Burns Unit. Examination revealed deep burns confined to the right upper limb. There was a deep circumferential burn of the entire forearm and wrist and a partial thickness burn of the hand. The finger tips were cyanotic and movement of the fingers was restricted. The patient's burned limb was observed for 4 hours during which time, in spite of elevation, there were signs of increasing circulatory embarrassment in the hand; the limb appeared to be under excessive tension (Fig. 1, *A*). Intravenous dye studies (20 c.c. of Disulphine Blue V.) showed marked diminution of blood supply to the hand. A single vertical incision down to deep fascia was made along the full length of the ulnar border of the forearm and wrist. The wound gaped widely (Fig. 1, *B*) and dye was seen to enter the hand. A pressure dressing was applied and covered with a light plaster of Paris shell. The limb was elevated. Re-dressing on the thirteenth postburn day showed healing of the hand and much of the forearm (Fig. 1, *C*). In order to allow maximum healing of partial thickness areas, grafting of full thickness components was delayed until the twenty-eighth postburn day. Granulating areas on the forearm were covered with strips of split thickness skin taken with a Humby knife from the right thigh. "Take" was essentially complete and the patient was discharged from the hospital following rehabilitation. Examination of this patient 6 months postburn revealed full function of the right upper extremity and an acceptable cosmetic appearance (Fig. 1, *D*).

CASE 2.—R. W., a 7-year-old boy, was admitted to the Burns Unit on the day of his injury. He had been walking across a smoking refuse dump when he fell, getting hot ashes inside his boots. Reportedly, the boots were removed at once. Examination on admission revealed full thickness burns of most of the circumference of the left leg and a part of the posterior thigh; there were also burns, mixed in depth, of the right knee and popliteal area. Several hours following admission, the left leg was noted to be tense and cold to touch and the foot was edematous and cyanotic (Fig. 2, *A*). This had occurred despite elevation of the limb. The patient was taken to the operating room and, under general anesthesia, Disulphine Blue V. dye was given intravenously. Little dye was seen to enter the left foot and decompression incisions were made on each side of the leg (Fig. 2, *B*). Subsequently, dye entered the foot. Although decompression appeared adequate, excision of the burn was performed following confirmation of burn depth in the well-demarcated area of full thickness loss. The latter procedure was carried out using a thigh tourniquet to effect a bloodless field (Fig. 2, *C*). A pressure dressing was applied to the limb and the burns of the opposite limb were dressed in the usual manner. On the ninth postburn day (Fig. 2, *D*) the area of excision was grafted with strips of split thickness skin taken from the thigh with a Humby knife. The grafts survived and the burns of the opposite limb healed without grafting. The patient was discharged to his home 3 months following injury. Fig. 2, *E* shows the involved leg one year postburn. There is no disability.

DISCUSSION

During World War II the importance of decompression of the crushed limb was well recognized. So, also, were the dangerous "tourniquet-effects" of the coagulation treatment of burns on the hands and fingers. We believe that Iverson's[6] remarks on the use of skintight plaster of Paris casts (to minimize edema) can be applied to the effect produced in circumferentially burned limbs: "There is . . . a real hazard in producing an unyielding encasement around a part which is becoming involved in edema, resulting in constriction of the vascular supply and necrosis of the finger tips." We have been able to find 3 references to decompression of constricting burns in the literature. Blocker,[2] speaking in a symposium on burns (Iowa City, Iowa, 1951), stated that, in circumferential burns of the upper limb with progressive hand swelling, he incised the burn down to deep fascia. Wallace,[8] reviewing the general

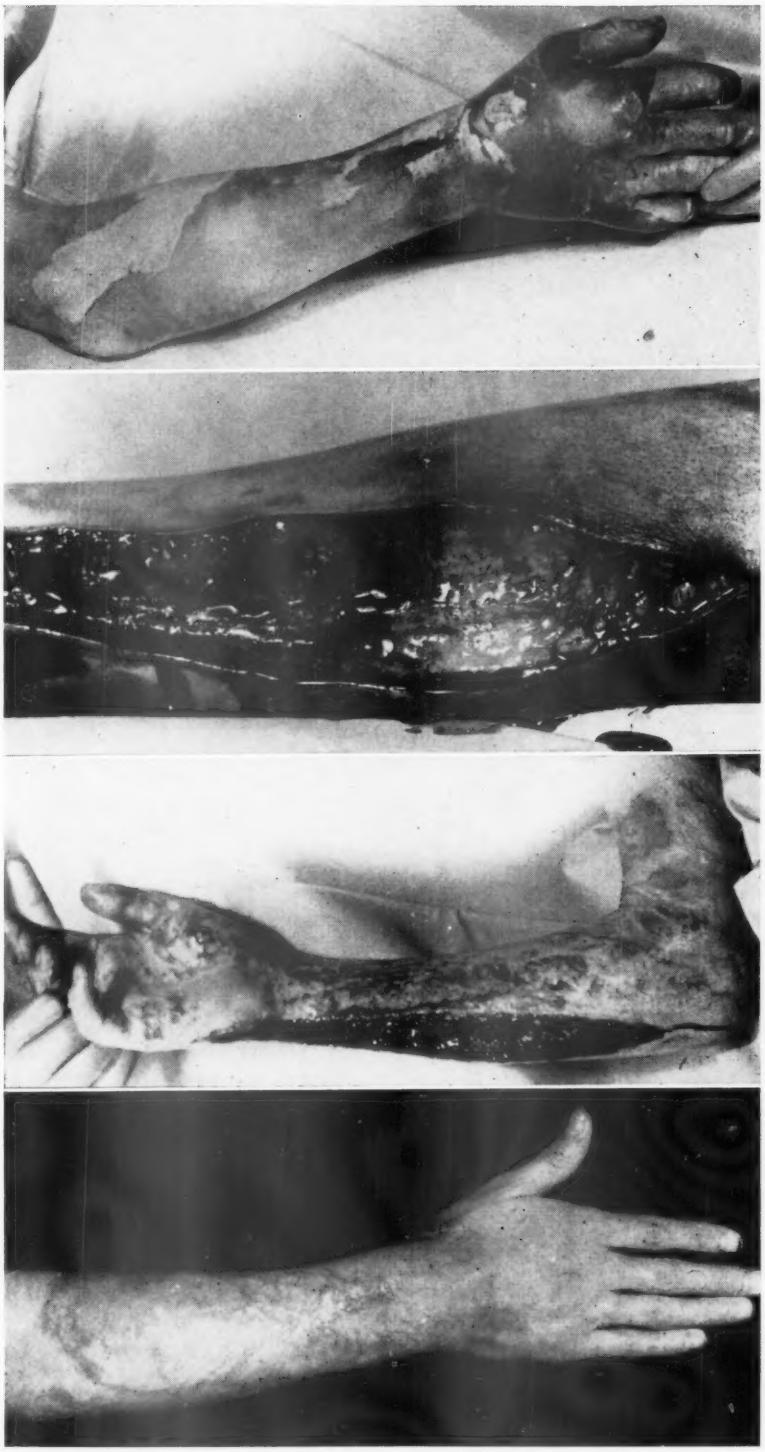

Fig. 1.—*A*, Burns of right forearm and hand 5 hours postburn. Note blanching of forearm and edema of hand. *B*, Close-up view of decompression incision (viewed from above) extending the full length of the forearm. Bulging of edematous subfascial tissue is evident but extension of incision through fascia was not necessary. *C*, Appearance of limb on thirteenth postburn day at time of first dressing change. Hand and much of forearm have re-epithelized. Residual full thickness areas and incisional wound were grafted 2 weeks later. *D*, Appearance of limb 6 months following burn.

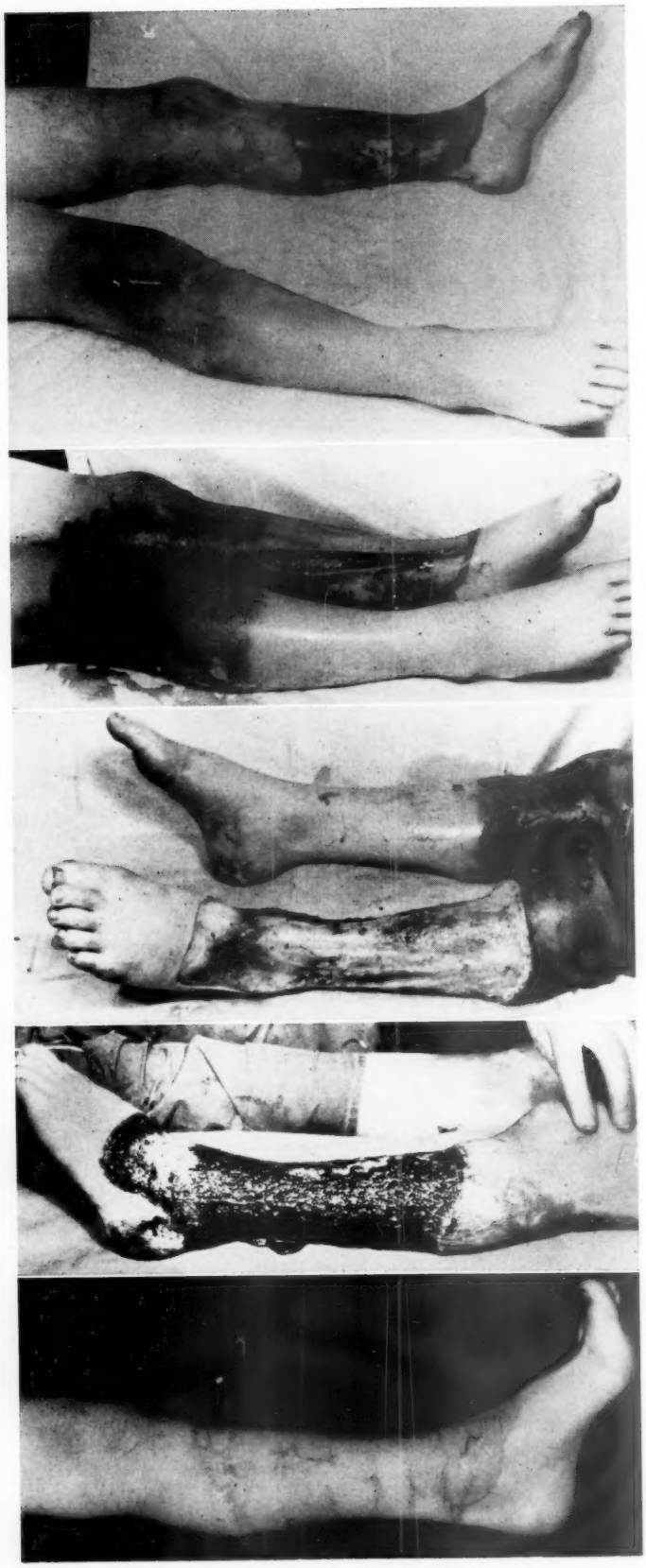

Fig. 2.— For legend, see opposite page.

problem of burns, mentioned using multiple incisions to relieve tension in 4 cases during a 2-year period. Recently, Evans[4] stated: "Involved limbs are, of course, suspended to reduce oedema, and the necessity of relieving incisions must be borne in mind where there are deep circumferential burns of the extremities." If decompression was indicated in any of the cases reported by Young,[10] Cope,[3] Whittaker,[9] or others advocating immediate excision of full thickness burns, it was certainly effected by this treatment.

Although a burned extremity is the most common site of the lesion requiring decompression, it should not be inferred that constricting burns cannot occur elsewhere on the body. Extensive burns of the neck and chest may, during the early postburn period, cause respiratory embarrassment. Although not a substitute for tracheostomy, multiple incisions through the burn will often ease this difficulty. Occasionally, burns of the scalp, particularly where one or both external ears are involved, will benefit from decompression. In one of our cases, early incision through the postauricular scalp transformed the appearance of the burned ear from blanched to red, with subsequent healing without deformity.

SUMMARY

1. The clinical features and pathogenesis of the constricting burn, usually a circumferential extremity burn, are described.

2. Methods of early operative decompression of these lesions are outlined.

3. Illustrative case reports are detailed.

4. Previous references to decompression are mentioned and applications of this principle to nonextremity burns are discussed.

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Fig. 2.—*A*, Demarcated full thickness burn of left leg, with partial thickness burns of knee and lower thigh as well as opposite knee. The left foot is swollen and dusky. *B*, View of lower extremities following dye injection and decompression of left leg full thickness burn. The lateral incision cannot be seen in this picture. The darkened appearance of both knees represents marked dye uptake in hyperemic partial thickness burns. *C*, Left leg following excision of deep burn under thigh tourniquet. Excision has been performed to include subcutaneous tissue down to deep fascia. *D*, Appearance of left leg 9 days postexcision. Leg grafted following cleansing of the granulating surface. *E*, Appearance of left lower extremity one year following injury. Return of function has been complete.

PLASMA ANTITHROMBIN ELEVATIONS IN BUCCAL VARIDASE-TREATED PATIENTS

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MOSELEY and associates[6] observed significant elevations in plasma antithrombin following aerosol trypsin therapy. In a previous study one of us[2] reported a direct quantitative relationship between plasma antithrombin and plasma trypsin. In clinical conditions associated with diminished blood trypsin, antithrombin titers were low (pancreatic cancer, fibrosis, and cystic fibrosis); high antithrombin levels were found in patients with increased entry of trypsin into the blood stream (acute interstitial, hemorrhagic, or necrotic pancreatitis). In a subsequent paper 2 of us[3] showed that the antithrombin phenomenon was an intravascular physiologic complex based upon an "antithrombinogen-trypsin" interaction.

The present investigation focuses attention upon a streptokinase-antithrombin relationship. In this study elevated antithrombin levels were obtained in hospitalized patients treated with small doses of buccally-given streptokinase for uninterrupted periods varying from 1 to 34 weeks.

MATERIALS

Blood samples were obtained from 18 patients under active streptokinase therapy for periods varying from 1 to 34 weeks. Another 18 normal individuals known to be free of liver or pancreatic disease served as controls and received placebo tablets for 1 to 34 weeks.

Buccal Varidase tablets containing 20,000 units of streptokinase (Lederle) were employed.* Controls received tablets of exact appearance but without streptokinase.

PROCEDURE

The method for determining plasma antithrombin levels has been published.[2, 3] Each patient had pretreatment antithrombin determinations and subsequent tests were made once weekly.

Buccal Varidase was administered 4 times a day; each single dose comprised 1 tablet.

The percentage of antithrombin elevation was determined by dividing the pretreatment antithrombin level into the level following therapy and multiplying by 100.

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*Buccal Varidase tablets were supplied by Lederle Laboratories, Pearl River, N. Y.

RESULTS

The results are listed in Table I.

TABLE I. ANTITHROMBIN LEVELS IN 18 BUCCAL VARIDASE-TREATED PATIENTS COMPARED WITH CONTROLS

PATIENT	TREATMENT (WEEKS)	ANTITHROMBIN ELEVATION (PER CENT)	
		TREATED	CONTROLS
1	1	+10	0
2	1	+14	0
3	2	+26	2
4	3	+18	0
5	4	+29	0
6	6	+17	0
7	6	+24	0
8	8	−14	2
9	10	+29	0
10	11	+30	0
11	12	+18	0
12	18	+22	0
13	22	+26	0
14	22	+17	0
15	24	−11	0
16	27	+29	0
17	32	+31	0
18	34	+28	0

DISCUSSION

In 16 of the 18 patients elevated plasma antithrombin levels appeared during the first week of uninterrupted buccal Varidase therapy and persisted throughout the treatment period. The magnitude of antithrombin elevation was 10 to 31 per cent, depending upon the frequency and duration of treatment. Moseley reported a much higher range of antithrombin elevation in aerosol trypsin-treated patients. Untreated controls showed zero to only 2 per cent elevation in antithrombin activity.

Several workers have reported elevated plasma antithrombin levels in patients with acute pancreatitis.[1, 4, 6] In these studies the range of antithrombin elevation above normal varied from at least 100 to over 500 per cent. In contrast, following continuous buccal Varidase therapy for as long as 34 weeks, the maximum antithrombin elevation observed was 31 per cent. It therefore appears that, in patients receiving buccal Varidase therapy, antithrombin elevation is well below the pancreatitis range.

SUMMARY

1. Plasma antithrombin was determined in 18 hospitalized patients under active, uninterrupted buccal Varidase treatment for periods varying from 1 to 34 weeks.

2. Following the first few days of buccal Varidase medication the plasma antithrombin activity rose. The range of antithrombin elevation was from 10 to 31 per cent.

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THE CLINICAL USE OF TEFLON TUBES AS A VASCULAR SUBSTITUTE FOR MAJOR ARTERIES

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PROGRESSIVE experience has indicated that synthetic fibers can be used satisfactorily as large and, in some instances, small vessel substitutes. In this laboratory, extensive experimentation has been carried out with homologous arterial grafts, venous autogenous and homologous grafts, as well as various synthetics.[6, 11, 15] Clinically, in addition to homografts and autogenous veins, synthetic materials including Orlon, nylon, Ivalon, and, more recently, Teflon have been used in this institution.

Because the procurement, method of processing, and storing of homologous grafts is cumbersome, as well as the observed development of degenerative changes, the search for better synthetic materials has continued.[1, 7] Nonpermeability, chemical inertness, low porosity, pliability, easy procurement, and sterilization are all desirable qualities for a plastic fabric to be used as a vascular prosthesis. Teflon, polytetrafluorethylene, is notable for its nonwettability, strength, relative impermeability, and low tenacity. Furthermore, the host response to Teflon in terms of fibroblastic response is notably minimal.[9, 12] The use of Teflon for chemical filters also attests to the inertness of this material. A comparison of the characteristics of Teflon with other synthetic materials which have been used for vessel substitution is presented in Table I.[10]

Table I

	TEFLON	NYLON	DACRON	ORLON
Tenacity (Gm./denier)	1.6-2.0	6.0-7.8	4.8-6.2	4.7-5.3
Tensile strength (lb./sq. in.)	50,000	88,000	90,000	75,000
Response to heat	High resistance	Sticky at 455° F.	Sticky at 455° F.	Sticky at 455° F.
Resistance to acids	Excellent	Poor	Poor to H_2SO_4	Poor to H_2SO_4
Resistance to alkalis	Excellent	Good	Poor	Poor
Solvent	None	Formic acid	Metacresol	Ethyene carbonate

The initial experimental work reporting the use of Teflon for arterial replacement from this laboratory has been published.[5] Teflon fabric grafts implanted in both the thoracic and abdominal aortas in 60 dogs resulted in overall graft success in 98 per cent when obvious technical errors are excluded, and

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92 per cent when all failures are included. These grafts were lined by thin, translucent, endothelial membrane and covered by a thin, fibrous layer on the outside. As "mature" grafts they were pliable and could not be burst even with intraluminal pressures of 500 mm. Hg; neither wrinkling, stenosis, nor calcification was found.

Impressed by the inherent qualities of the material when woven into a fabric and by the experimental results, we considered clinical trial to be indicated. To our knowledge, this is the first clinical experience with this material reported in the literature.

CLINICAL EXPERIENCE

In the initial 2 cases, grafts were fabricated from T-8[5] material after the proper measurements had been made. These grafts were cut to size and the flat fabric was manufactured into tubes by means of a portable sewing machine. In the last 9 cases, seamless tubes of Teflon became available to us. We are indebted to Mr. John B. Sidebotham* for his collaborative efforts in manufacturing Teflon thread to specification into seamless tubes of low porosity. These seamless Teflon tubes are available in a wide range of sizes measured and identified by their compressed diameter. The smaller tubes are 8, 10, 13, and 15 mm. in diameter; the large tubes come in sizes of 20, 25, 30, 35, 40, and 45 mm.

General Procedure.—After isolation of the vessels to be anastomosed, both proximal and distal, a clamp is applied momentarily to these areas. The transverse diameter measured in the clamp is noted in millimeters.

The seamless tube of correct diameter and slightly greater than approximate length is washed in hot water with a surgical detergent soap, with particular attention to the inner lining. After rinsing carefully approximately 3 times for a total period of 10 minutes, the material is autoclaved and is then immediately ready for use. A cuff of approximately 4 mm. is rolled back. The cuff edge is sutured to the proximal vessel, utilizing a running whipstitch of the ordinary variety. After completion of the proximal anastomosis and with the distal graft being occluded, the proximal arterial clamp is released temporarily to fill the graft with blood. The graft is thus allowed to sweat for a few seconds. The proximal arterial clamp is reapplied and the blood is allowed to exude from the end. The graft is cut for length and treated in a similar fashion distally with an everted cuff to be utilized in the anastomosis of the distal vessel or vessels.

More recently, however, to insure against graft leakage during heparinization of the patient, 50 c.c. of the patient's blood is removed by syringe from the aorta and injected into the Teflon tube for preclotting. In order to avoid spontaneous distal thrombosis, 20 to 40 mg. of heparin is injected into the lower aorta with the proximal clamp in position but unclamped. After one or two beats, the proximal aorta is occluded followed by occlusion of the iliacs, then excision of the aorta is carried out, followed by graft replacement. The rationale of the use of heparin in this manner is to insure an exceedingly high concentration in the lower extremities during proximal occlusion for protection against

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distal spontaneous thrombosis; yet a dose of heparin, when carried into the general circulation upon restoration of normal flow, will not produce total heparinization. Leakage through a preclotted graft has been practically nonexistent when utilizing this plan of partial heparinization. Lee-White clotting time studies are undertaken the day prior to operation to determine more accurately the clotting curve obtained with a single dose of 30 mg. of heparin in the individual patient. These curves vary considerably from patient to patient and the dosage utilized at surgery will be reduced or elevated empirically depending upon the curve obtained with the test dose.

More recently (Case 7), a preclotted Teflon graft was used in a patient with an aneurysm in the descending aorta who was placed on partial extracorporeal bypass. The patient was totally heparinized (2 mg. heparin per kilogram of body weight). With total heparinization there was practically no sweating through the fabric of the preclotted Teflon graft.

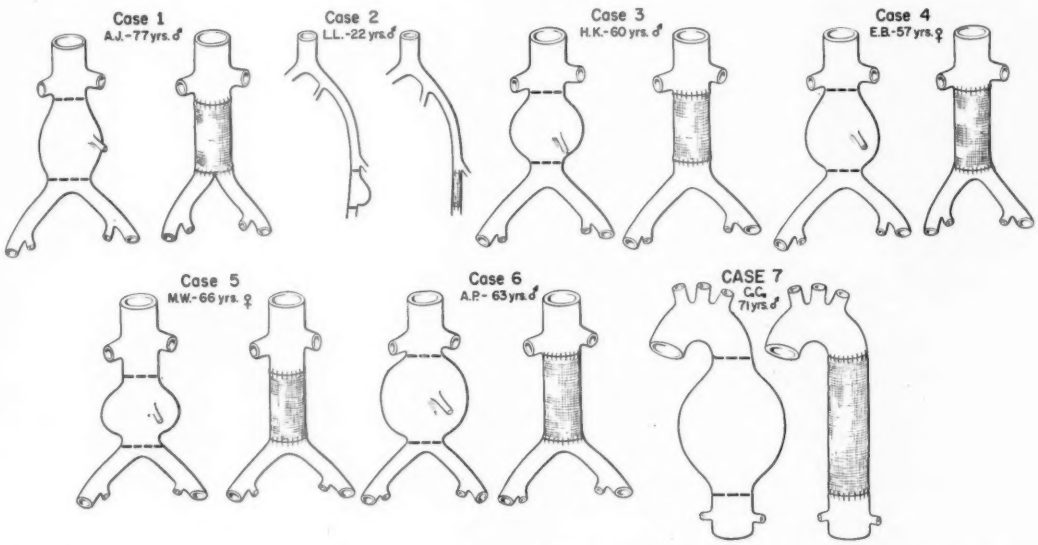

Fig. 1.—Seven aneurysms replaced with Teflon tubes of varying width and length (see text).

CASE REPORTS

ANEURYSMS (Fig. 1).—

Case 1.—A. J., a 77-year-old white man, was admitted to the hospital Oct. 18, 1955, with a mass in the mid- and infraumbilical area of his abdomen which had become progressively more painful during the 5 weeks prior to admission. On the day following admission, an infrarenal abdominal aortic aneurysm was resected and replaced with a seamed Teflon tube 17 cm. long and 4.5 cm. in compressed diameter. The distal anastomosis was to the conjoined common iliac arteries which were sutured together along their medial sides to make a new bifurcation. The patient was discharged on the ninth postoperative day with normal femoral pulsations. A laparotomy was performed 2½ months later to lyse adhesions producing partial small bowel obstruction. The graft was covered by smooth, thin peritoneum and was easily indented. He has remained well since the last operation.

Comment: This is the first patient in whom Teflon fabric was used as a vessel substitute. At this writing he is 22 months postoperative and doing well. The technique of anastomosing the distal portion of the graft to the united common iliac vessels is that introduced by Poth[13] (Fig. 2, *A*).

Case 2.—A. L., a 22-year-old white man, was admitted to the hospital on Dec. 13, 1955, with an aneurysm of the left superficial femoral artery secondary to a gunshot injury in that area 8 years ago. This had suddenly enlarged to 9 or 10 cm. in diameter and had become painful about 6 weeks previously. On Dec. 16, 1955, a false aneurysm was removed, including 4 cm. of involved superficial femoral artery. The defect was bridged by a seamed Teflon tube, 4 cm. long and 0.8 cm. in diameter. He was discharged on Dec. 21, 1955, with improved pedal pulses and a warmer left leg and foot.

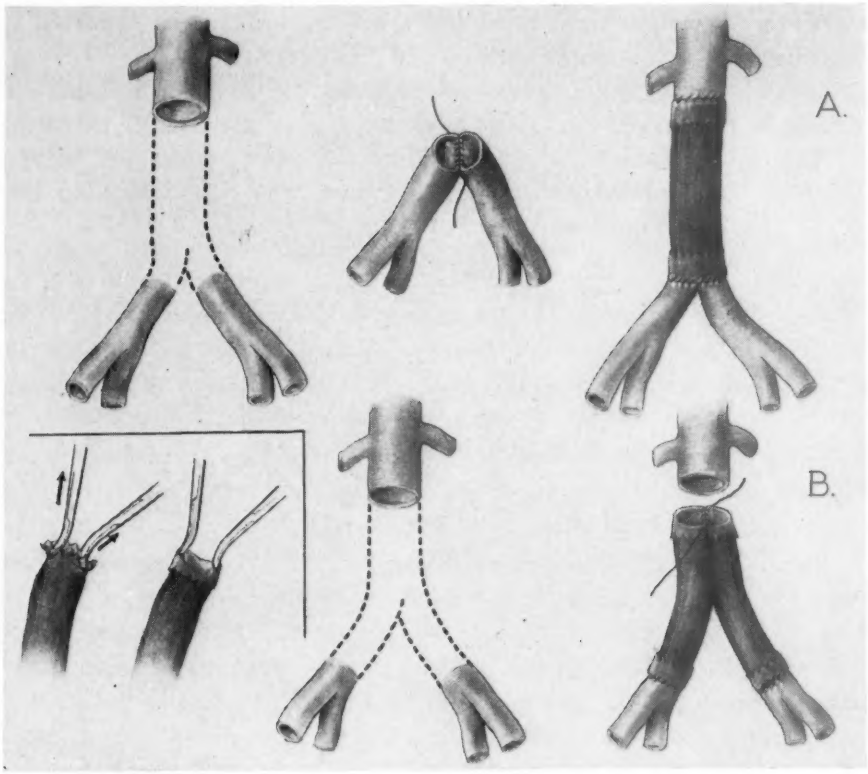

Fig. 2.—*A*, After excision of aortic bifurcation, if there has been no need for extensive excision of the common iliacs, the latter may be mobilized and joined together by medial suture. Thus, only a single tube is needed for substitution of the aorta and bifurcation. *B*, If the common iliacs have been excised so that they cannot be joined after mobilization, 2 separate tubes of Teflon are sutured to the iliacs. The proximal Teflon tubes are sutured together on the medial side and anastomosed as a single tube to the proximal aorta. Insert shows the manner of everting the cuff utilizing 2 mosquito clamps.

Comment: Recent examination revealed good pulsations throughout the leg. The patient is a laborer who wrestles as a hobby and admits to no complaints.

Case 3.—H. J., a 54-year-old white shipyard worker, was first seen on July 24, 1956, because of a large, football-sized, pulsatile, abdominal mass projecting mainly to the left. Peripheral pulsations were intact. X-rays revealed a calcified rim to the aneurysm. An intravenous pyelogram demonstrated functioning kidneys bilaterally. The position of the aneurysm in the upper abdomen suggested the possibility of renal artery transplantation. The patient did not admit to any symptoms referable to the aneurysm. On July 31, 1956, the aneurysm was excised immediately below the take-off of the right renal artery, and a seamless Teflon graft, 2.5 cm. in diameter and 13 cm. long, was inserted. The distal anastomosis was made to the aorta 2 cm. proximal to its bifurcation. The postoperative convalescence was uneventful and the patient was discharged home on the ninth postoperative day. Examination 12 months after surgery revealed no complaints and excellent bilateral peripheral pulsations.

Case 4.—E. B., a 70-year-old woman, experienced back pain and a pulsatile abdominal mass for one year. On Feb. 19, 1957, abdominal exploration revealed a fusiform aneurysm from the infrarenal area to 1 cm. proximal to the bifurcation of the aorta. A seamless Teflon graft, 12 cm. long and 20 mm. wide, was inserted with preservation of the most distal aortic segment and bifurcation. Forty milligrams of heparin was injected prior to clamping the aorta. Minimal oozing occurred due to the heparin effect. Follow-up 5 months later disclosed good pulses and no subjective back pain.

Comment: This was one of the smallest proximal abdominal aortas encountered in terms of diameter. Having available multiple-sized seamless tubes from which to choose for replacement is important.

Case 5.—M. W., a 66-year-old woman, experienced claudication of the right hip, thigh, and calf on walking 2 level blocks which was relieved by rest. There were no pulses in the right leg, and fair pulses in the left leg. Abdominal aortic pulsation was excellent. Percutaneous femoral arteriograms revealed a fair distal arterial bed with no segmental occlusive disease present. At laparotomy on June 5, 1957, for the express purpose of exploring the right iliac vessels, a 5 by 6 cm. aortic aneurysm was found. After resection, a seamless Teflon graft, 8 cm. long and 25 mm. wide, was inserted preserving the aortic bifurcation. Thirty milligrams of heparin was injected at the time of reconstitution of flow through the preclotted graft. The entire right iliac artery was severely arteriosclerotic down to the common femoral artery. A right lumbar sympathectomy was carried out.

Comment: Although pulses did not return in the right leg, the patient has a warmer leg and foot with marked improvement of the claudication syndrome; pulses are good in the left leg. Improvement in this patient's leg may be in part due to the lumbar sympathectomy. We postulate, however, that by eradicating the dilated aorta, we improved blood flow through the narrowed arteriosclerotic vessels distally. With a uniformly dilated aneurysm without thrombotic laminations, it is possible that the systolic pulse was dissipated in the aneurysm. By replacing an inexpansible conduit it is possible that this pulse pressure was restored and may account in part for her improvement.

Case 6.—E. P., a 63-year-old man with emphysema, was admitted to the hospital on July 18, 1957, with complaints of weight loss and a pounding pulsatile sensation in the abdomen for 4 months. At operation, a large fusiform aneurysm extending from the infrarenal area to the bifurcation was found. Resection of the aneurysm was carried out down to, but preserving, the bifurcation, and a seamless Teflon tube 8 cm. long and 35 mm. wide was inserted. Because of a moderately prolonged clotting time response to the test dose of 30 mg. of heparin given the day before operation, only 20 mg. of heparin was injected into the distal vessels. The patient was discharged home in 10 days with good leg pulses.

Comment: As in Cases 4 and 5, the aortic segment just proximal to the common iliac arteries could be spared and simple proximal and distal anastomoses carried out.

Case 7.—C. C., a 71-year-old man, was admitted to the hospital on Sept. 6, 1957, with complaints of severe dyspnea and chest pain. Posteroanterior and lateral chest x-rays disclosed a posterior mediastinal mass contiguous with the thoracic aorta. An angioaortogram with 90 per cent Hypaque solution confirmed the diagnosis of a fusiform aneurysm extending from a point one inch distal to the left subclavian artery to the level of the diaphragm. On Sept. 11, 1957, through 2 separate left thoracotomy incisions, the fifth and ninth ribs were excised, exposing a 10 by 15 cm. aneurysm.

Blood (50 c.c.) was aspirated from the aneurysm and a Teflon tube of suitable length and diameter was preclotted. The patient was totally heparinized with 130 mg. of heparin. The pericardium was opened and a catheter was placed in the left atrium; a similar catheter for aterial input was placed in the previously exposed left common femoral artery. Using ¼ inch Tygon tubing, the 2 catheters were connected to each other through a Sigmamotor pump. After aortic bypass was started, the aorta was clamped distal to the subclavian artery and immediately above the diaphragm. The diaphragm had been previously stripped downward for adequate exposure. Pressures in the upper half of the body were monitored

by means of a previously placed catheter in the right radial artery. While the proximal aortic pressure rose somewhat, it was adequately regulated by the speed of the Sigmamotor pump.

The aneurysm was excised and replaced by the preclotted seamless Teflon tube (15 cm. long and 4 cm. in diameter). The total period of bypass was 71 minutes. The flow rate varied between 1,400 and 1,600 c.c. per minute (22 c.c. per kilogram per minute). During this period the patient manufactured 30 c.c. of urine. The operation was concluded with reconstruction of the femoral artery and chest closure and protamine reversal of the heparin effect.

Postoperatively no neurologic defect was evident and urine output was excellent. There was a transient rise in blood urea nitrogen from 16 to 29 mg. per cent on the third postoperative day which had returned to 12 mg. per cent on the sixth day. A repeat angioaortogram 2 weeks postoperatively revealed a straight isodimensional thoracic segment at the site of replacement (Fig. 3). The patient was discharged on the fifteenth postoperative day.

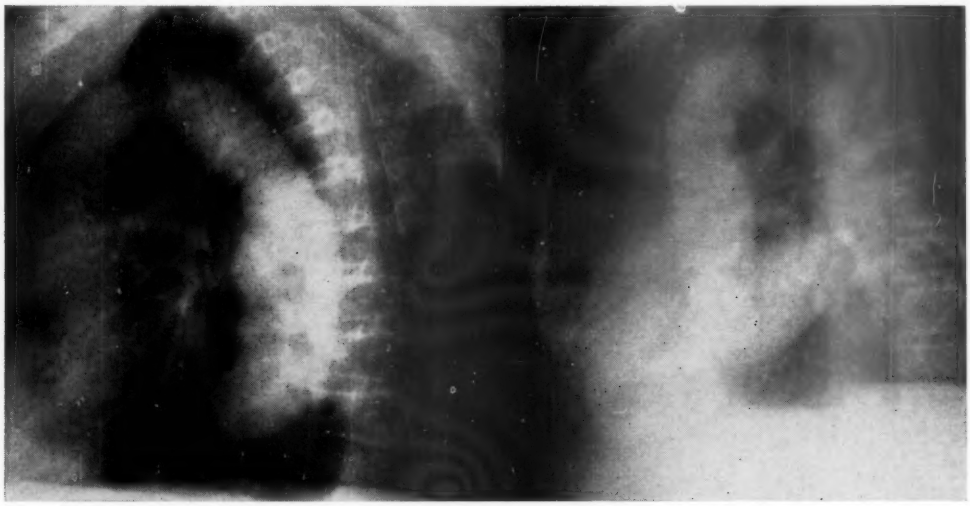

Fig. 3.—Case 7 (C. C.). The above photographs represent pre- and postoperative angioaortograms. The descending thoracic aneurysm has been replaced with a seamless Teflon tube extending from the aortic arch to the diaphragm.

Comment: The aortic bypass technique described by Cooley and co-workers[2, 3] successfully allowed aneurysm resection without spinal cord damage.

It is significant that no "sweating" of blood occurred through the preclotted Teflon graft in spite of total heparinization. Only 2 additional sutures were needed at the line of proximal anastomosis. Thus, the use of a preclotted Teflon graft appears safe in the face of total heparinization.

OBLITERATIVE DISEASE SECONDARY TO ARTERIOSCLEROSIS (Fig. 4).—

Case 8.—L. S., a 48-year-old white man, was admitted to the hospital on Nov. 22, 1955, complaining of severe cramping pain in his right leg and thigh of 2 weeks' duration brought on by walking one block. This pain occasionally would awaken him at night. His right foot was cold and tender. A femoral arteriogram showed complete block of the superficial femoral artery down to the middle portion of the popliteal artery. On Dec. 6, 1955, a seamed Teflon graft, 0.8 cm. in diameter and 57 cm. long, was placed subcutaneously in his right thigh bridging the obstruction from common femoral to popliteal arteries. End-to-side anastomoses were made at each end. Pedal pulses were palpable postoperatively and the patient was discharged on Dec. 20, 1955, free of claudication. He was readmitted on Dec. 24, 1955, with a cold right foot and return of claudication. No pulses were palpable below the common femoral artery, and the upper thigh incision was deeply indurated and somewhat tender. The patient was afebrile. On Dec. 30, 1955, a right lumbar sympathectomy

was performed. This relieved his leg cramps but did not improve the capillary circulation nor warmth of the right leg. The indolent infection in the right thigh became more overt and was drained on Jan. 3, 1956, grossly appearing to be a hematoma, but beta hemolytic streptococcus was cultured. Drainage persisted in spite of antibiotics. The Teflon bypass graft was removed on Jan. 12, 1956. The graft was not occluded but had become detached proximally. The common femoral artery was now occluded by a thrombus. The femoral arteriotomy was closed with arterial silk after the thrombus was removed, restoring blood flow into the deep femoral artery. An antibiotic-resistant staphylococcal infection now was present in the upper thigh incision. Small intestinal obstruction developed on Jan. 31, 1956, finally necessitating a laparotomy to correct an intestinal volvulus. The same staphylococcal infection attacked the abdominal incision, causing a partial separation. This was slowly healing, and the patient appeared to be improving, when he suddenly expired.

Autopsy showed multiple aneurysms of the distal aorta with one of the right common iliac artery which ruptured and caused a fatal exsanguination. Septic infarcts were found in spleen, kidneys, and lungs. There were mural thrombi in the inferior vena cava.

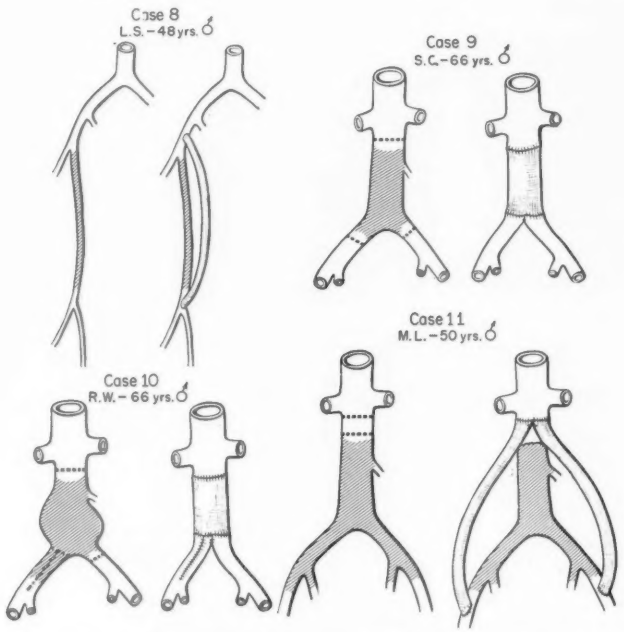

Fig. 4.—Four cases of obliterative vascular disease with vessel segments replaced or bypassed with Teflon tubes.

Comment: This initial attempt at bypass in the extremity possibly resulted in failure because of the surgeon's technical shortcomings and judgment rather than failure of the material. It is of interest that the Teflon bypass was not occluded by thrombus; however, it is possible that if a clot were present, the infection may have resulted in its lysis. While Teflon tubing can be used for bypass in the extremity when no joint crease must be bridged, it is our present feeling that it is not a satisfactory substitute in the extremity.

Case 9.—S. C., a 66-year-old white man, was admitted to the hospital on April 20, 1956, complaining of weakness and claudication in the right leg and thigh after walking one block. An aortogram revealed total occlusion of the distal aorta and proximal part of the right common iliac artery. Good peripheral drainage was shown. On April 27, 1956, a bilateral lumbar sympathectomy and a resection of the distal aorta and proximal right common iliac artery were performed. A 1.5 cm. wide and 8.2 cm. long seamless Teflon tube was sewn into place, again anastomosing distally to the revised iliac bifurcation. Good femoral pulses and faint pedal pulses were palpated postoperatively. He was discharged on the seventeenth postoperative day with warm feet and has continued to walk without claudication.

Case 10.—R. W., a 66-year-old white man, had claudication of the right thigh and calf for 2 years. An aortogram on Nov. 20, 1955, showed total occlusion of the distal aorta and right common iliac artery. A good peripheral arterial bed was demonstrated. After the aortogram, the patient complained of pain in the right flank. An intravenous pyelogram showed no excretion from the right kidney. His blood urea nitrogen rose from 10 mg. to 58 mg. in 7 days; therefore, no definitive treatment could be undertaken. At 6 months his blood urea nitrogen was normal, but his right leg and thigh had atrophied markedly, necessitating a cane for ambulation. On May 25, 1956, a bilateral lumbar sympathectomy, a right common iliac thromboendarterectomy, and excision of a thrombosed and aneurysmal distal aorta were carried out. A seamless Teflon tube, 2.5 cm. in compressed diameter and 10 cm. long, was used for a graft. Again, the distal anastomosis was made to the conjoined and shortened common iliac arteries. A thrombus was removed from the endarterectomy site shortly after the grafting was completed and good circulation was restored to the legs. The patient succumbed about 24 hours postoperatively of an anterior wall myocardial infarction but demonstrated a patent graft without local complications at autopsy.

Comment: This case exemplifies a complication of aortography. In addition, it again profiles the diffuse nature of the disease for which the patient was operated upon. In spite of a thorough work-up, the complication causing death was unexpected.

Case 11.—M. L., a 50-year-old man, had progressive claudication of the hips, loss of libido, and nocturnal leg cramps. An aortogram showed occlusion of the distal aorta and common iliac arteries, but all arteries distal to the external iliac arteries were patent. On June 12, 1956, a bilateral lumbar sympathectomy was performed and a bilateral bypass Teflon graft was inserted. The aorta was transected just proximal to the thrombosis. Two pieces of 1.5 cm. seamless Teflon tubing were sutured together medially to form a bifurcation; then the combined outer circumference of these tubes was anastomosed to the proximal aorta. The Teflon tubes were then anastomosed end-to-side to the external iliac arteries just proximal to the inguinal ligaments. The right tube was 27 cm. long and the left was 30 cm. long. Good femoral pulses and normal capillary filling in the feet were demonstrated. The patient was able to walk about 4 blocks comfortably at the time of discharge on June 30, 1956, and is still well.

Comment: The bifurcation, manufactured by suturing the medial edges of 2 separate Teflon tubes, functions as well as the conjoined iliac arteries, is easy to construct, and is leakproof (Fig. 2, *B*).

DISCUSSION

Seamless Teflon fabric is soft, pliable, and technically easy to handle. The finest atraumatic needle utilized for arterial suture penetrates the 2 thicknesses of a cuff seam as readily as it passes through a single layer. The material is easily procured, inexpensive, can be stored and transported without difficulty, and is adaptable to any number of situations. In our installation, various sizes of Teflon seamless tubing in yard lengths are kept in supply in ordinary cupboards. The greatest increase in diameter between these various sizes is 5 mm.; consequently, the greatest disproportion that can exist between the vessel to be anastomosed and the fabric is 2.5 mm. A difference of this magnitude is a minor item and is readily compensated for in the anastomosis. At operation, after a few measurements, the proper diameter fabric is chosen and autoclaved after washing.

This report deals only with the use of tubes. Experiments are in progress in this laboratory evaluating bifurcation grafts made of the same material[14]; however, clinical experience to date indicates little need for a bifurcation graft. The valuable contributions of Poth to this problem have shown that by reconstruction of the vascular channels only a straight tube is necessary.[13] If, for

example, only a few centimeters of the common iliacs need be sacrificed, the distal vessels may be mobilized so that they may be conjoined by a medial suture which results in a single lumen. The medial partition (anteroposterior) is composed of the full thickness of each common iliac. Thus, only a straight tube is needed for anastomosis to the proximal aorta and the distally joined iliacs. The single distal anastomosis which is technically easy replaces 2 anastomoses necessary for bifurcation grafts. In effect, the aortic bifurcation has been moved caudad (Fig. 1, Case 1). On the other hand, if the length of the common iliacs removed makes it impossible to suture them together, 2 separate straight tubes are anastomosed one to each common iliac end-to-end or end-to-side (Fig. 4, Case 10). Proximally, the fabric of the 2 tubes is joined by suture medially, so that a common opening is achieved for anastomosis to the aorta. Thus, the effect is that of elevating the aortic bifurcation to the subrenal area. These reconstructions of anastomotic channels have been without fault in our experience.

Consequently, for straight segments of the aorta from the left subclavian artery down to the celiac axis and from the renals down to and including the common iliacs, Teflon grafts fill the need admirably. As a multipurpose graft, however, where a curvature in the vessel exists, such as in the transverse aortic arch, an extremity bypass graft, or where there is the need for an anastomosis of various vessels into the graft, Teflon fabric grafts are presently inadequate. Actually, the latter situation may be a temporary one; further collaboration of surgeons with weavers may result in the development of satellite apertures with as much length as necessary on straight segment graft.

Since 1954 homografts have been available to us for clinical use. After a year's experimentation with Teflon fabric, it appeared that this prosthetic vessel graft better satisfied our needs in the clinical situation than did homografts. Consequently, during the past year we have not inserted homografts in the aorta below the renals, preferring the use of Teflon prosthetics. Uncertain with regard to the final result, work up to the present time indicates that the eventual result may be better than with homografts. Of interest is the recent observation that Teflon fabric implanted in the experimental animal tends to gain strength with time in contrast to other synthetic materials. In addition, experimental work in the growing pig reveals a lack of demonstrable calcification or other degenerative changes observed in homografts and other synthetics.[4] Recently, it has been demonstrated that treated Teflon tends to become endothelized more rapidly than the untreated material as utilized in these cases. While this is desirable, no difficulties have been encountered clinically because of delayed endothelization.[8]

SUMMARY

A heterogeneous group of 11 patients with abdominal and thoracic aortic aneurysms and/or obliterative arteriosclerotic disease has been subjected to resection and/or bypass utilizing Teflon prosthetics as vascular substitutes. In the first 2 cases these grafts were fabricated with seams; in subsequent cases seamless tubes were used.

In 7 elective operations for aortic aneurysm there has been no death. In the total group of 11 cases an 18 per cent mortality was encountered. Neither death appeared to be related to the graft material. One death followed an acute myocardial infarct; the second occurred as a complication of wound infection in the operative area.

Seamless Teflon (polytetrafluorethylene) tubes have intrinsic qualities suitable for vascular replacement. It is a satisfactory substitute for straight segments of the descending thoracic aorta and the subrenal abdominal aorta including the iliacs.

Because of the multiple advantages of Teflon in cost, availability, indestructibility, chemical inertness, ease of sterilization, the assurance of an isodimensional anastomosis, the ease in suturing, and the absence of graft failures to date, we have utilized by preference this material as a vascular substitute for the specific areas indicated.

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ADDENDUM

Since submission of this report, 2 additional patients have had abdominal aneurysms replaced with Teflon seamless tubes without event.

THE EFFECT OF SUTURE MATERIAL IN DETERMINING THE PATENCY OF SMALL ARTERY GRAFTS

A Comparison Study Using Silk, Nylon, and Dacron Arterial Suture Material

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INTRODUCTION

MOST experimental artery graft studies emphasize the difficulties in obtaining patent grafts when such are used to replace segments of arteries whose lumens are less than 5 mm. in diameter. The majority of authors[7, 8, 9] suggest thrombus and occlusion of the graft to be a frequent source of failure. One of us (J. T. P.) observed in previous studies that thrombus formation usually occurred within one hour following insertion of the artery graft (Fig. 1). In addition, the thrombus appeared to have its mode of origin at the suture line and adjacent intima of the homograft and host artery (Fig. 2).

Accordingly, this paper concerns the replacement of segments of small arteries measuring 4 mm. or less in their inside diameter and compares the short-term results when arterial silk, nylon, and Dacron suture materials were used to create the anastomosis, with emphasis on the ability of the graft to maintain a patent lumen.

EXPERIMENTAL STUDY

Methods.—Three different types of femoral and/or carotid artery grafts were used in this study. They were (1) fresh autografts, (2) fresh homografts, and (3) homografts sterilized with beta-propiolactone and preserved in Ringer's solution and 10 per cent plasma at 4° C. The artery homografts were removed from mongrel dogs and measured 5 cm. or more in length. In each instance the cross-sectional diameter was 4.5 mm. or less.

A total of 66 small artery grafting procedures was performed. Segments of femoral and carotid arteries were excised and replaced as with near isodimensional grafts as was feasible. In each instance the inside diameter of the host artery measured less than 4 mm.

The anastomosis between the artery graft and host artery was made in an end-to-end fashion, utilizing an over-and-over suture with interruption of the suture line following completion of the posterior row.

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Three different types of arterial suture material were employed. They were 5-0 silk, 5-0 nylon (trade name, Ethilon) and 5-0 Dacron (trade name, Mersilene).* No appreciable difficulties were encountered in using Dacron or nylon when compared with the conventional silk suture. It was our opinion

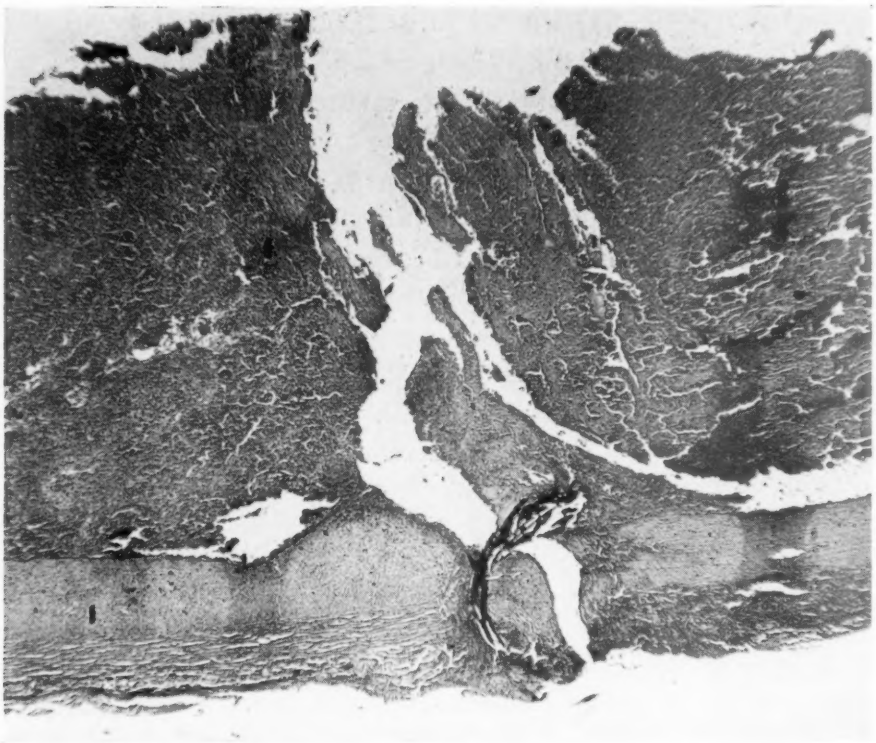

Fig. 1.—Photograph illustrating the origin of a thrombus in an artery homograft used to replace a segment of a small artery. The origin of the thrombus appears to arise at the anastomotic site.

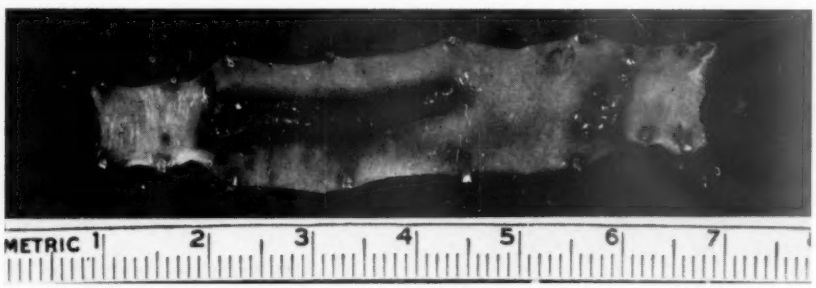

Fig. 2.—Photomicrograph demonstrating the thrombus attachment at the suture line and adjacent intimal surface of the artery homograft and host artery.

that nylon was the easier of the 3 suture materials to manage. Excessive bleeding at the suture line, once restoration of blood flow was established, was considered about equal for all 3 suture materials and in each instance was easily controlled by gentle pressure.

*The suture materials used in these experiments were kindly donated by Mr. C. W. Norman, Product Director, Ethicon, Inc., Sommerville, N. J.

RESULTS

The results of this experiment are shown in Tables I, II, and III. Four dogs expired within 4 days after the surgical procedures and are included in this report. The remaining animals were sacrificed at varying intervals ranging from 3 days to as long as 60 days, with the average being 30 days.

As seen in Table I, whenever a fresh artery autograft was employed as the replacement graft and irrespective of the type of suture material used in securing the anastomosis between the graft and host artery, a patent graft was observed. The one failure occurred in the animal that developed a secondary wound infection.

TABLE I. FRESH ARTERY AUTOGRAFTS EMPLOYED IN REPLACING SEGMENTS OF SMALL ARTERIES

SUTURE MATERIAL	NUMBER	RESULTS
Silk	6	6 patent
Nylon	5	5 patent
Dacron	4	3 patent 1 occluded (wound infection)

In 23 instances (Table II), a fresh homograft was used to bridge the artery defect; 18 failures were due to partial or complete occlusion of the grafts. The small number of patent grafts observed in this group did not appear to be related to the suture material per se; however, nylon and Dacron appear to have slight, but hardly significant, numerical superiority.

TABLE II. FRESH ARTERY HOMOGRAFTS EMPLOYED IN REPLACING SEGMENTS OF SMALL ARTERIES

SUTURE MATERIAL	NUMBER	RESULTS
Silk	7	1 patent 6 occluded
Nylon	8	2 patent 6 occluded
Dacron	8	2 patent 6 occluded

Table III shows the results when a preserved artery homograft was employed to establish the continuity of the peripheral artery. Only 3 of the 28 grafts remained patent. In the 2 successful grafts observed, nylon was the suture material employed in creating the anastomoses. Again the number of patent grafts does not appear significant.

TABLE III. PRESERVED ARTERY HOMOGRAFTS EMPLOYED IN REPLACING SEGMENTS OF SMALL ARTERIES

SUTURE MATERIAL	NUMBER	RESULTS
Silk	12	1 patent 11 occluded
Nylon	7	2 patent 5 occluded
Dacron	9	9 occluded

DISCUSSION

It became quite apparent during the course of this study that factors other than suture material used in anastomosing the host artery and the artery

graft were responsible for determining the patency of the small artery grafts. In this regard, a number of authors[3, 5-7, 9] have implicated the ever-present problem of constriction and narrowing of the artery lumen whenever an end-to-end anastomosis is employed. Under such conditions, turbulent blood flow and increased intraluminal pressure result from the constriction. It has been suggested that such events precipitate intravascular thrombosis.[12] Holman[5, 6] has written extensively on this subject, and in a series of experiments demonstrated the superiority of a Z-plasty type of anastomosis in small artery surgery, so as to enlarge the lumen at the anastomosis. He is supported in part by Mavor[7] who has reported a high degree of success with small artery homografts by employing an end-to-side method of anastomosis between the host artery and the artery homograft. By such a maneuver, the anastomosis is greatly enlarged when compared to the conventional end-to-end method performed under similar circumstances.

Other conditions, such as preservation and storage of artery grafts and the type of graft, have been suggested as factors that influence the patency of small artery grafts. At present, Heirtonn[4] is of the opinion that freeze-dried artery homografts appear to be less susceptible to thrombus formation than grafts preserved by other media. Moore,[9] however, has achieved a greater number of patent small artery homografts when employing alcohol as the method of preservation. A publication of interest in this regard was the report by Sawyer and Pate[10, 11] who demonstrated that a difference of potential exists between the intima and adventitia of fresh artery homografts and the host artery. Such a phenomenon has been suggested to attract the negative charged erythrocytes and hence incites thrombus formation. In addition, they demonstrated that freeze-dried homografts did not show this difference of potential. Much of their data, however, was obtained by employing segments of the thoracic and abdominal aorta.

To add further controversy to the subject, Anzola[1] has shown that the freshness of the small artery homograft tends to improve the results in small artery grafting procedures. In addition, Baker[2] has reported a 100 per cent degree of success when fresh autografts were used in replacing segments of the carotid artery. It is of interest that our study complements Baker's findings with fresh autografts and in a like manner compares favorably with Anzola's study[1] with fresh homografts.

From our experiments and the available data of others, it is suggested that (1) the type of artery graft, (2) the method of artery homograft preservation, and (3) the technique in preventing constriction at the anastomotic site are some of the factors that play important roles in preventing thrombotic occlusion from occurring in small artery grafting procedures. Needless to say, others' indeterminable sources interplay with one another in this problem. The suggestions of Moore[9] relating to oblique end-to-end anastomosis between the artery graft and the host artery and the use of anticoagulants during the immediate postgrafting period are worthy of investigation. From our study, the 3 different

suture materials, namely silk, nylon, and Dacron, did not appear to influence the patency of artery homografts when used to replace segments of small arteries with inside diameters of less than 4 mm.

CONCLUSION

We have studied the effect of 3 different types of arterial suture material, namely silk, Dacron, and nylon, in constructing the anastomosis between the artery graft and host artery in replacing segments of small arteries with inside diameters measuring less than 4 mm.

It is concluded that the types of suture material used in this experiment played little or no part in determining the patency of the small artery homograft.

A discussion of some of the factors that contributed to the patency of these grafts has been presented.

We wish to acknowledge the technical assistance of Mr. Marcus Ravnan and Mr. Wilbert Heimann.

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ARTERIOGRAPHIC ERRORS IN LOCALIZATION OF ACUTE ARTERIAL OBSTRUCTION

Case Report and Experimental Studies

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THE importance of prompt diagnosis and treatment of acute arterial obstruction is well known. Accurate localization of the obstruction is necessary, especially when surgery is to be done. Aortography and arteriography are useful adjuncts to diagnosis in cardiovascular disease but will not always show accurate localization of an acute arterial obstruction. If acute obstruction occurs in an artery, a static column of blood exists between the point of obstruction and the next significant proximal branch. Sufficient concentration of contrast media for roentgenologic visualization will not be present in such a static column of blood unless injected directly into the area (Fig. 1). The following case report and laboratory studies confirm this observation.

CASE REPORT

L. G., a 56-year-old white man, was admitted to the Surgical Service at Grady Memorial Hospital one hour and 15 minutes following the onset of sudden pain and numbness in the right leg. History revealed a previously described cardiac arrhythmia of several months' duration. No diagnosis or treatment for this abnormality had been established. Physical examination revealed a pulse rate of 92, which was irregular, and a blood pressure of 140/80. Except for cardiac enlargement and arrhythmia, the examination of the chest and abdomen were negative. Normal color, temperature, and pulses were present in all extremities except the right leg. There was mottled cyanosis of the foot and coolness below the knee on the right. Pulses were absent below the proximal popliteal artery of the right leg.

An electrocardiogram revealed auricular fibrillation. An arteriogram was performed by percutaneous injection of 20 c.c. of 30 per cent Urokon† into the common femoral artery. The results were interpreted as showing occlusion of the distal superficial femoral artery (Fig. 2). On the basis of these arteriographic findings, it was elected to explore the superficial femoral artery. Under spinal anesthesia, an anteromedial incision was made at the mid-thigh level. The embolus was not found, and the wound was closed. The patient was then repositioned and an embolus in the popliteal artery was removed. Color, warmth, and pulses returned to normal immediately.

Certain difficulties experienced in the operative management of this patient prompted laboratory evaluation of arteriography in acute arterial obstruction.

TECHNIQUE

Six mongrel dogs were anesthetized with intravenous pentobarbital. Through a low midline abdominal incision, the distal aorta was exposed. A

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†Urokon-sodium acetrizoate, Mallinckrodt Chemical Works, St. Louis, Mo.

curved Potts clamp was applied to the anterior one-half of the aorta just proximal to the trifurcation, and a longitudinal incision was made into the lumen. After inserting a lead pellet, the arterial incision was closed with everting continuous silk sutures (Fig. 3).

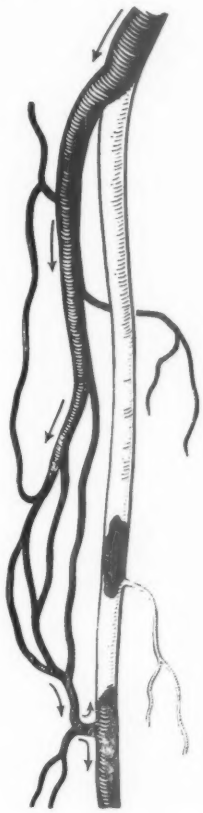

Fig. 1.

Fig. 2.

Fig. 1.—Distribution of flow of blood in femoral arterial system with acute obstruction.
Fig. 2.—Arteriogram of patient with popliteal embolus interpreted as occlusion of distal femoral artery.

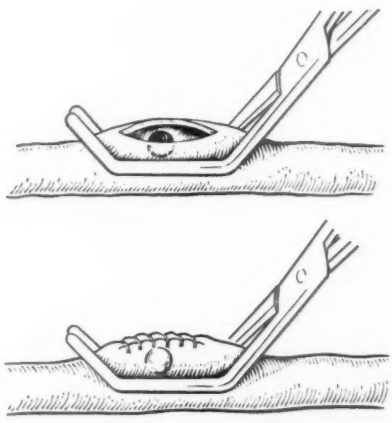

Fig. 3.—Method of insertion of artificial emboli into the aorta of dogs.

Fig. 4.—Artificial embolus in the popliteal artery of a dog.

Fig. 5.—Arteriogram with embolus in right femoral artery; bilateral partial constriction previously produced (note left femoral artery).

Fig. 6.—Artificial embolus in the proximal portion of the superficial femoral artery of a dog.

While manually occluding the caudal artery, the Potts clamp was released, and the embolus was carried by arterial blood flow into one of the extremities.

Following the release of the embolus, a polyethylene tubing was inserted in a cephalad direction into the caudal artery and advanced until the tip could be felt in the distal aorta. The tubing was secured by a ligature on the caudal artery. The free end of the tubing was brought out through a stab wound in the inguinal region and clamped. The abdominal wound was closed with interrupted silk sutures.

Arteriograms were obtained by the injection of 10 to 15 c.c. of 30 per cent Urokon through the polyethylene tubing into the aorta. This method produced excellent arteriograms demonstrating an embolus with obstruction in one leg of the animal, and the opposite extremity for control observations.

In one dog the site of lodgment of the embolus was predetermined by partial constriction with ligatures about both femoral arteries (Fig. 5).

RESULTS

In all animals in which the obstruction was complete, a segment of the artery proximal to the obstruction was not visualized with the arteriograms (Figs. 4, 5, and 6). Subsequent autopsy failed to reveal any thrombosis to account for this lack of filling. Five animals were examined less than 24 hours after obstruction by the embolus, and the other animal was examined at 48 hours.

Immediately distal to the point of obstruction, there was a segment of artery which usually did not fill with contrast media, although the vessel more distally was occasionally visualized as the contrast media returned to the main channel by collateral pathways.

The vessels obstructed in this study were the common femoral, superficial femoral, and popliteal arteries.

DISCUSSION

Early surgical removal of acute arterial emboli is widely advocated.[1-5, 7, 9, 10] Accurate localization of the obstruction is necessary to minimize unnecessary and sometimes harmful dissection of a vessel. It has been suggested by Lovingood and Patton,[5] and Julian and Dye[4] that translumbar aortography and/or arteriography will confirm the diagnosis without delay and accurately localize the point of occlusion.

In the case reported here, the physical findings suggested a popliteal embolus, but arteriography indicated the point of obstruction to be in the superficial femoral artery. The interpretation of arteriographic findings in this patient, however, led to unnecessary surgical exploration of the superficial femoral artery. This could have been detrimental, since valuable collaterals might have been interrupted and vasospasm increased. In this instance, the end results were, fortunately, satisfactory for the patient.

In every complete obstruction produced in animals, there was a segment of artery proximal to the obstruction not visualized with arteriography. This

was apparently due to a static column of blood proximal to the point of obstruction. This static column of blood has been mentioned by de Takats[2] as a point of early proximal thrombosis, but this was not the reason for nonfilling in the dogs in this study.

Emboli often obstruct an artery in one branch of a bifurcation. When this occurs there is no static column of blood. This may explain the accurate results reported by Lovingood and Patton, and Julian and Dye.

In cases of trauma, the diagnosis of arterial injury is usually evident with the loss of pulse and the change in temperature. However, the exact point of injury is not always well defined, and arterial spasm may confuse the physical findings. Trippel[8] discussed the role of spasm in arteriography. It appears that the relationship of spasm to trauma and arteriography has not been adequately determined.

Studies with arteriography in trauma by Lumpkin and associates[6] have shown that arteriography may be important in more accurately evaluating vascular injury. However, in acute obstruction in trauma, as with emboli, the presence of a proximal static column of blood must be considered in interpretation of the arteriograms.

SUMMARY

1. The importance of early localization of an embolus obstructing an artery is well established.

2. A case report is presented which demonstrates certain inaccuracies of arteriography.

3. Obstruction was produced in 6 mongrel dogs by introducing arterial emboli, and laboratory studies resulted in arteriograms which reveal a segment of artery proximal to the obstruction not visualized with contrast media.

4. Arteriography has not proved to be totally dependable in the localization of acute arterial obstruction.

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BLOOD STUDIES IN THE HYPOTHERMIC DOG

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INTRODUCTION

IN THE last few years the mechanism of the blood diathesis resulting from body cooling has interested an increasing number of investigators. Impaired coagulation as a serious complication of hypothermia has been emphasized by some[10] and denied by others.[3] Investigators variously report that in hypothermia in dogs, clotting time may increase, show no change, or decrease.

We have analyzed blood of dogs before hypothermia, during hypothermia, and in the recovery phase with regard to the coagulation mechanism, blood elements, and plasma proteins and have made correlated microcirculatory observations.

MATERIALS AND METHODS

Fourteen adult mongrel dogs averaging 17.2 Kg. in weight were used. The animals were wormed and placed on an adequate diet supplemented with vitamins and minerals (Vitamycin) for at least one month before the experiments. Food was withheld 12 hours prior to cooling. While the animal was under pentobarbital sodium (Nembutal) anesthesia (0.44 grains per kilogram of body weight), a tracheal tube was inserted through the mouth. The control (or prehypothermic) blood sample was withdrawn from a leg vein. An incision along the linea alba permitted exteriorization of a small portion of mesentery for microscopic circulatory observation by quartz rod transillumination. The exposed mesentery was continually bathed with mammalian Ringer's solution at a temperature of 37° to 38° C. A Leitz stereoscopic microscope was used with magnifications of 50×, 100×, and 150×. Following microscopic observations of circulating blood, the mesentery was replaced and the abdominal incision closed and sealed.

The animal was immersed in a 4° C. water bath. Positive pressure breathing of air was instituted when rectal temperature reached 30° C. on an average. When rectal temperature was between 24° and 28° C., the animal was removed from the ice bath and exposed to room temperature of about 30° C. but rectal temperature continued to drop from 1° to 4° C. The second (or hypothermic) blood sample was taken when the temperature had reached

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its lowest at a range between 21° and 26° C. with an average of 22° C. Artificial respiration was discontinued when the animals could maintain spontaneous respiration, usually at rectal temperatures of 28° to 31° C. The animal was allowed to warm by its own processes, shivering being suppressed by occasional small intravenous doses of Nembutal. Immediately after the hypothermic blood sample was taken, the abdomen was reopened and the mesentery placed again for periodic microscopic observation. The temperature of the mammalian Ringer's solution bathing the mesentery was adjusted to the animal's rectal temperature. During the warming phase, the third blood sample was withdrawn at body temperatures sampling the range from 26° to 38° C. with an average of 32° C. and ranging in time from 4 to 23 hours after immersion in the ice bath.

Blood samples (30 ml. each) were obtained from leg veins; blood was allowed to flow through an 18-gauge needle coated with Arquad-2C into siliconized syringes. Blood without any anticoagulant was transferred to siliconized tubes for the determination of McCleery's clotting time[12] and to glass test tubes for Lee and White clotting time (2 tubes), for prothrombin consumption determination, and clot retraction according to Stefanini's methods.[15] Blood smears were made for differential leukocyte counts. Blood containing disodium sequestrene as an anticoagulant was used for the following determinations: platelet and erythrocyte count in Rees and Ecker's diluent following Quick's procedure,[14] platelet thromboplastic factor according to Stefanini's method,[16] and total leukocyte count using a diluent of 5 per cent acetic acid containing a few drops of gentian violet. Oxalated blood was employed for Quick's prothrombin time using Simplastin, Wintrobe's sedimentation rate and hematocrit, Sanford's erythrocyte fragility test, and the tyrosine determination for fibrinogen.[14] Oxalated plasma was used for electrophoretic analysis. Venous blood was collected in heparin for the pH determinations.[8] The blood pH indicated that our procedure of ventilation was adequate in maintaining a pH reasonably close to the prehypothermic value.

Aliquots of plasma were prepared for dialysis promptly after the blood samples were taken. A Veronal buffer of pH 8.5 and ionic strength of 0.1 was used.[20] One volume of plasma was diluted with 2 volumes of buffer and dialyzed against 2 changes (350 ml. each) of buffer for a total of 48 hours at a temperature of 2.5° C. Electrophoresis was carried out at 0.8° C. in a 2 ml. Tiselius cell with a potential gradient of 11.1 volts per centimeter for a period of 72 minutes.

Electrophoretic patterns were photographed by the use of a modified Philpot-Svensson optical system. Enlarged tracings (4×) of the descending boundaries were made on graph paper and the areas of the peaks measured with a planimeter. Tracings of the upper and lower limits of each pattern were made and the average of the 2 measurements was used as the unit of area.[13] In separating the various peaks for measurement, perpendiculars were dropped to the base line from points of inflection of the curves with the exception of the gamma globulin and fibrinogen peaks, in which case the procedure of Pedersen[17] was used. The alpha peaks were 4 in number, but since

the separation of the individual peaks was quite arbitrary, they were analyzed individually and also as a single component migrating between the beta globulin and albumin peaks. Because the junction of the alpha 1 and albumin peak is somewhat variable, the trailing edge of the albumin peak was continued in a symmetrical fashion to the base line and the alpha 1 peak measured between this curve and the neighboring perpendicular.[20]

All data in these experiments were subjected to statistical analysis. The data on the control blood samples were compared with those of the hypothermic and warming phase blood samples by determining Student's t and obtaining the level of confidence of the hypothermic and warming phase population belonging to the control population. A level of confidence above 95 per cent was considered significant.

Fig. 2 is based upon a statistical analysis of the results of the coagulation tests. The mean of the dogs' minimum temperatures is represented at 22° C. The first half of each plot, in the cooling phase, is derived by converting the mean control value and the regression line value of the hypothermic and warming phase samples at 22° C. to percentage change from the control. The second half of each plot, in the warming phase, is the regression line derived from the hypothermic and warming phase samples converted to percentage change. The regression equations for the warming phase are: (t = body temperature)

PTT (platelet thromboplastic time) = $-3.45 + 0.838t$
PCT (prothrombin consumption time) = $-6.27 + 1.15t$
PC (platelet count) = $-230.9 + 14.5t$
PT (prothrombin time) = $9.27 + 0.00844t$
CT (clotting time) = $190.6 + (-4.58t)$.

RESULTS

Coagulation Studies.—Tables I, II, and III include only the data from those experiments in which the determinations were performed on all 3 blood samples. (The results from those animals in which only the first 2 blood samples were available were similar to samples I and II shown in Tables I, II, and III.) In Tables I and II, means and ranges are shown. All dogs, except one, had an increase in clotting time during hypothermia as compared to their prehypothermic values (Table I). The exceptional dog did not show a change in coagulation time (silicone) and this accounts for the low value of 30 minutes in the hypothermic range. The next lowest clotting time in the second sample was 53 minutes. During the warming phase, the clotting time again approached normal and reached its control value in those animals whose third blood sample was taken relatively close to normal body temperature.

The results of the Lee and White clotting tests in glass tubes were similar to those in silicone tubes (Table I). However, the total time for coagulation and the difference among the 3 samples were much less in the glass tubes than in silicone tubes.

The platelet counts were extremely low in the hypothermic animals. Each dog showed this decrease. As the animals warmed, the platelet counts progressively approached their control values, and in the dogs in which the third sample was taken at a body temperature close to normal, the platelet count was the same as the control sample. The usual correlation was found between platelet count and clot retraction (Table I).

The results of the prothrombin time tests are shown in Table I. There was an average decrease of 0.7 second in prothrombin time in the second sample. This difference is not considered to be significant. The prothrombin time of the third sample was usually found to be between the prehypothermic and hypothermic values.

The prothrombin consumption time (Table I) was shorter in the second blood sample than in the control. During the warming phase, the prothrombin consumption increased and in 5 of the 7 animals exceeded the control values. In those 5 animals in which the consumption time of the third sample exceeded the prehypothermic values, the third blood sample was taken at a body temperature close to normal.

The platelet thromboplastic factor test revealed a significant decrease in the platelet thromboplastic activity as the result of body cooling (Table I). The animal with the highest hypothermic value, that is, the 27.4 seconds seen in Table I, was the dog which, as mentioned before, did not show a change in clotting time. The next highest hypothermic value was 17.2 seconds. During the warming phase, the platelet thromboplastic activity approached or exceeded the normal value and thereby paralleled prothrombin consumption. Those animals in which the prothrombin consumption times of the third sample exceeded their normal values also showed a higher than normal platelet thromboplastic activity in the third sample.

TABLE I. SUMMARY OF COAGULATION TESTS

DETERMINATION	NUMBER OF DOGS	I PREHYPOTHERMIA		II HYPOTHERMIA		III WARMING PHASE	
		MEAN	RANGE	MEAN	RANGE	MEAN	RANGE
Clotting time, silicone (minutes)	9	37	18-49	110	30-166	41	28-67
Clotting time, glass (minutes)	7	13.5	5.9-21.2	19.9	10.0-25.4	12.3	6.6-21.4
Platelet count (thousand/cu.mm.)	11	365	222-444	90	60-126	279	112-448
Clot retraction (ml./hr.)	7	1.09	0.9- 1.4	0.20	0.1- 0.4	0.96	0.6- 1.3
Prothrombin time (seconds)	11	8.9	6.0-11.5	8.2	5.5- 9.7	8.7	6.2-11.5
Prothrombin consumption time (seconds)	7	30.6	22.5-35.5	18.0	13.6-23.5	31.8	20.3-40.3
Platelet thromboplastic factor (seconds)	7	22.3	13.8-27.3	15.6	10.5-27.4	23.1	13.5-34.3
Fibrinogen (mg. per cent)	11	413	257-579	449	249-708	498	278-784

Plasma fibrinogen determinations (Table I) did not show a significant change between the prehypothermic and hypothermic blood samples. However, the warming phase blood sample did show a slight increase in fibrinogen in

all but one dog and this increase was greatest in those dogs whose third samples were taken close to normal body temperature. The exceptional dog, which had a progressive decrease in fibrinogen, accounts for the 278 mg. per cent in the third blood sample range.

Blood Elements.—The hematocrit readings and erythrocyte counts are summarized in Table II. The hematocrit exhibited a progressive increase in all 3 samples, 21.7 per cent between the first and second sample and 26.0 per cent between the first and third sample. The erythrocyte count demonstrated an increase of 14.9 per cent between the first and second blood sample and 32.3 per cent between the first and third sample. The difference in slope of the erythrocyte count increase and the hematocrit increase can best be explained on the basis of the range of error in the counting of erythrocytes. It was noted that in the dogs in which the third blood sample was taken within 10 hours after immersion in the ice bath and when their body temperatures were less than 30° C. the hematocrit showed a decrease between the second and third samples, while if the interval was greater than 10 hours and their body temperature was above 30° C. the third sample showed an increase in hematocrit.

In 10 dogs the measurement of sedimentation rate indicated a decrease between the first and second samples but this proved to be an increase of rate in 9 of the 10 when corrected for hematocrit differences. Six of the 10 dogs did not show any sedimentation in the third blood sample. The corrected sedimentation rate on the other 4 dogs showed an increase to a point greater than their control values.

The total leukocyte count is greatly decreased in hypothermia and approaches normal during the warming phase (Table II). In the differential leukocyte count the percentage of lymphocytes shows a significant increase in hypothermia and returns to normal upon warming. The percentage of neutrophils and eosinophils exhibits a significant increase in hypothermia. The neutrophil percentage returns to or exceeds its control value in the warming phase while the percentage of eosinophils continues to decrease (Table III).

The erythrocyte fragility test did not show any change from sample to sample in any dog.

TABLE II. SUMMARY OF HEMATOCRIT AND CELL COUNT

DETERMINATION	NUMBER OF DOGS	I PREHYPOTHERMIA		II HYPOTHERMIA		III WARMING PHASE	
		MEAN	RANGE	MEAN	RANGE	MEAN	RANGE
Hematocrit (corp. vol.%)	11	46.5	34.5-54.0	56.6	45.0-65.0	58.6	46.0-66.5
Erythrocyte count (thousand/cu.mm.)	11	5,929	4,790-6,530	6,815	3,870-8,440	7,747	5,260-9,760
Total leukocyte (per cu.mm.)	11	9,645	3,720-18,930	1,755	700-3,650	6,518	920-16,200

Plasma Electrophoresis.—The use of electrophoresis in the present experiments was undertaken primarily to determine what changes occur, if any, in the total and/or relative concentrations of the plasma proteins between the normal

and hypothermic blood samples. The routine procedure in the evaluation of electrophoretic Schlieren diagrams was used to compute the concentration of each of the plasma components from the ratio of its area to the total area exclusive of the epsilon boundary. The electrophoretic analyses of the pre-hypothermic and hypothermic plasma samples of 8 dogs are summarized in Table IV. There was no consistent or significant change between the first and second samples in the total or individual components of plasma protein concentrations (Fig. 1). One dog possessed an extremely high gamma globulin

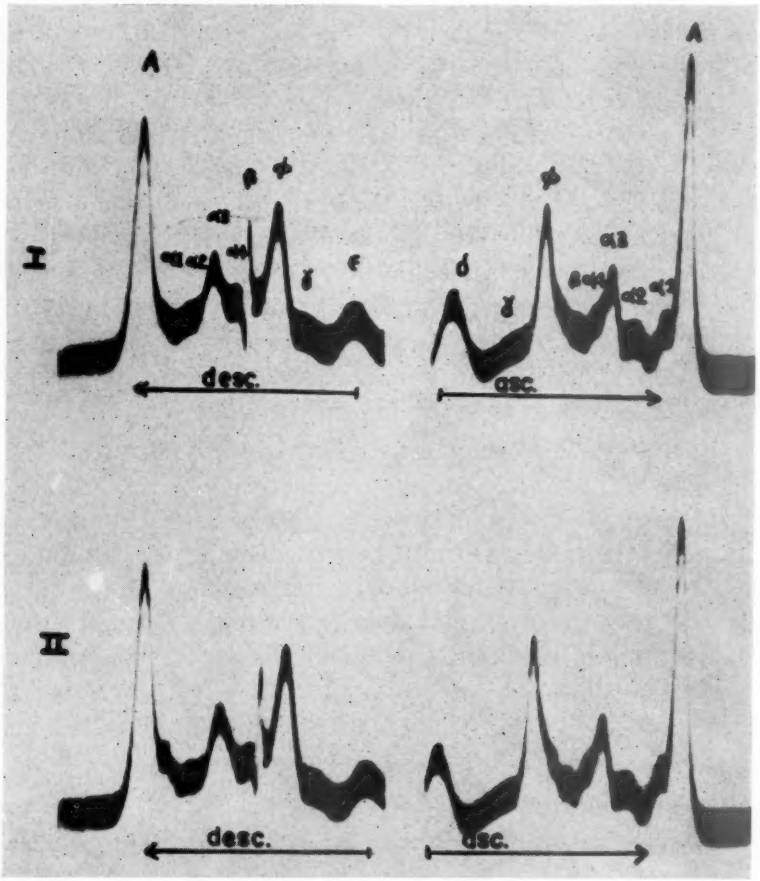

Fig. 1.—Electrophoretic patterns of dog DQ-137. The upper patterns (I) represent the normal plasma sample. The lower patterns (II) are from the hypothermic plasma sample.

TABLE III. DIFFERENTIAL LEUKOCYTE COUNT
(Average of 11 Dogs)

	I PREHYPOTHERMIA		II HYPOTHERMIA		III WARMING PHASE	
	COUNTS/CU.MM.	PER CENT	COUNTS/CU.MM.	PER CENT	COUNTS/CU.MM.	PER CENT
Neutrophil	7,089	73.6	1,198	68.4	5,078	78.0
Stab	183	1.9	28	1.6	222	3.4
Eosinophil	357	3.7	47	2.7	78	1.2
Basophil	10	0.1	2	0.1	0	0.0
Lymphocyte	1,678	17.4	423	24.1	952	14.6
Monocyte	309	3.2	54	3.1	183	2.8

content as indicated by the high values given in the range of the prehypothermic and hypothermic samples (27.40 and 29.87 per cent). The next highest value for gamma globulin in the prehypothermic samples was 13.79 per cent and for the hypothermic samples 16.47 per cent.

TABLE IV. ELECTROPHORETIC ANALYSIS
(Average of 8 Dogs)

	I PREHYPOTHERMIA (PER CENT OF TOTAL AREA)		II HYPOTHERMIA (PER CENT OF TOTAL AREA)	
	MEAN	RANGE	MEAN	RANGE
Gamma globulin	13.23	8.94-27.40	13.95	7.95-29.87
Fibrinogen	14.35	10.64-18.84	13.78	8.60-19.88
Beta globulin	5.21	2.88- 6.85	5.04	3.66- 7.00
Alpha 4 globulin	4.93	2.81- 8.60	4.91	3.91- 7.20
Alpha 3 globulin	10.22	3.08-16.53	10.43	2.65-16.99
Alpha 2 globulin	6.22	4.40- 7.95	6.27	4.50-11.23
Alpha 1 globulin	6.02	3.47- 9.30	4.68	2.93- 6.38
Albumin	39.82	26.60-53.82	40.95	27.29-51.88
Total area*	1,033.1	950-1,167	1,042.6	956-1,161

*In planimeter units.

Microscopic Circulatory Observations.—In general, the picture of the prehypothermic blood deviated from Knisely's interpretation of normal,[11] if at all, only in that a few white blood cells were seen hesitating and creeping on venule walls, and in a few animals occasional small agglutinated masses of erythrocytes and sometimes occasional large masses were seen in slow-flowing venules of small diameter (15 to 25 micra).

In the 14 dogs observed, the most noticeable mesenteric circulatory changes which occurred when the rectal temperatures ranged from 21° to 26° C. were as follows: (1) a great reduction in flow rate seen in both arterioles and venules, (2) a cessation of flow in many capillary beds while blood flowed via the arteriovenous anastomoses, (3) an apparent hemoconcentration which was most noticeable in venules of 40 micra or larger, (4) an increased number of white blood cells sticking to the walls of venules, (5) agglutination of erythrocytes into small and large clumps, both of which were seen in arterioles and venules, and (6) the appearance of cell-free plasma-filled spaces between clumps of flowing erythrocytes in the smaller vessels. This development of intravascular agglutination of erythrocytes, in various degrees, occurred in all but one dog. The dog which did not display intravascular agglutination of erythrocytes as a result of cooling is the animal which, as mentioned before, had an abnormally high concentration of gamma globulin as revealed by the electrophoretic studies. This same dog also showed the high leukocyte count of 18,930 in the prehypothermic range (Table II). It also had a high sedimentation rate and a low hematocrit.

During the warming phase an increase in flow rate, decrease in the number of white blood cells sticking to venule walls, and an opening of capillary circulation were the most noticeable changes from the observations during hypothermia.

DISCUSSION

Fig. 2 summarizes the results of the coagulation studies in 7 dogs in which the determinations were performed on all 3 blood samples. The other dogs in this study show similar results, although the information is not complete in each of these animals. The clotting time is prolonged in hypothermia and then approaches or falls below normal upon warming. The prothrombin time indicates that the factors necessary for normal coagulation, other than thromboplastin and calcium, are unchanged or slightly increased in the hypothermic plasma sample as compared with the normal. Since the prothrombin activity is within normal range, it is probable that the coagulation deficiency is caused by a lack of thromboplastic activity or calcium. Since Bigelow and co-workers,[2] Fisher and associates[7] and Fleming[8] have reported that the calcium level does not change in hypothermia, it is apparent that the prolonged clotting time is caused by a reduction of thromboplastic activity. This conclusion is supported by the observation of the decreased prothrombin consumption shown in Fig. 2.

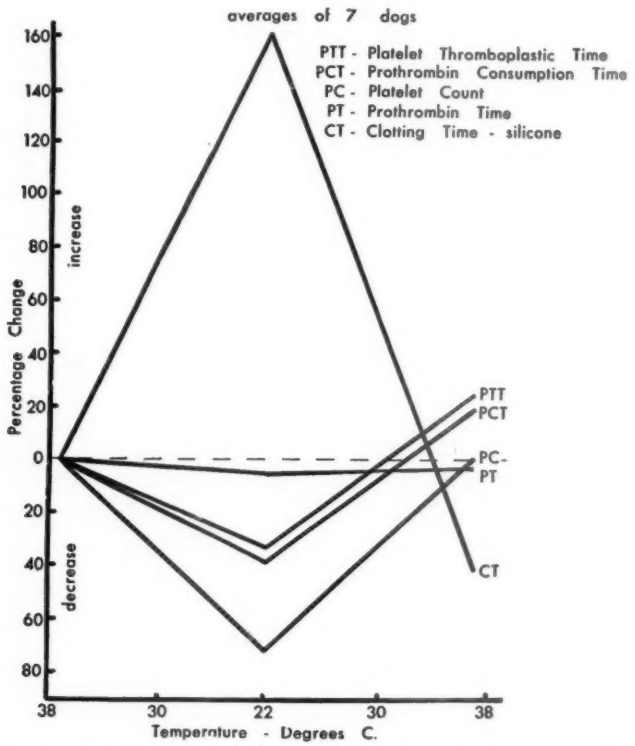

Fig. 2.—A statistical summary of the results of the coagulation tests.

It is necessary, therefore, to determine which of the thromboplastic components is deficient in causing the increase in clotting time, the plasma thromboplastins or the platelet thromboplastic factor. The 75.3 per cent reduction in the number of platelets predicates a decrease in the total platelet thromboplastic activity. Such a decrease is confirmed by the results of the platelet thromboplastic factor test. In order to determine whether the plasma thromboplastic

factors are also reduced in hypothermia, canine platelet extract and calcium were added to the animals' decalcified plasma in several experiments. It was found then that the clotting times were the same in the normal and hypothermic samples. The results of these coagulation tests, therefore, indicate that the prolonged clotting time in hypothermia is due to a reduction of platelets.

Upon return to normal body temperature, the clotting time reveals a hypercoagulability, and the prothrombin consumption and platelet thromboplastic factor exceed their normal values (Fig 2). This hyperactivity may be caused by an increase in the plasma concentration of the requisite factors during the later period of the warming phase as a result of water loss from the kidneys[1] and lungs (an artificial respirator is employed during most of this time). This suggestion is supported by the observation of an increased fibrinogen level and an increased hematocrit during the late warming phase. It was noticed in our animals in which the third blood sample was taken at a relatively cool temperature that the hematocrit showed a decrease as compared to its hypothermic value. On the other hand, those hematocrits taken at a late period during the warming phase showed an increase over the hypothermic hematocrit.

Our conclusion that platelet reduction is responsible for the prolonged clotting time in hypothermia is supported by the general agreement that platelets are reduced in hypothermia and return to normal upon warming.[3, 4, 6, 18, 19]

It has been observed in this study that there is only a low correlation between the number of platelets and the platelet thromboplastic activity when results from one dog are compared with those from another. The platelet count, therefore, is not a fully satisfactory index of platelet thromboplastic activity in dogs.

In our microcirculatory observations we found a prominent increase in the number of white cells sticking to venule walls in the hypothermic mesentery, and preliminary studies of tissue taken at autopsy from hypothermic animals have thus far shown an unusually large number of white cells apparently adherent to vessel walls. Villalobos[19] has investigated the very striking decrease in leukocytes and platelets during hypothermia and their rapid return to normal upon warming of the animal. It is his conclusion that the platelets and probably the white blood cells are "sequestered" but not destroyed during hypothermia, the liver and spleen being responsible for much of this sequestration. On the basis of our observations and those of Villalobos it seems indeed likely that the rapid disappearance of platelets and white cells is due to their sticking to vessel walls during hypothermia. Their release from these sites during the warming periods accounts for their rapid return to normal levels.

Our in vivo observations of mesenteric vessels during hypothermia also reveal an apparent hemoconcentration in venules of 40 micra and larger but an apparent increase in the proportion of plasma present in many vessels smaller than 40 micra in diameter. Increased hematocrit during hypothermia

supports the observation of hemoconcentration in larger venules. Crosby[4] reports that a preliminary experiment "seemed to indicate that the change in hematocrit was due to a temporary loss of plasma from the circulating blood." D'Amato and Hegnauer[5] postulate that the plasma lost during hypothermia has been trapped in minute peripheral vessels from which erythrocytes are excluded. While we recognized an apparent increase in plasma volume in the vessels smaller than 40 micra, it is possible that this increase in plasma volume is more apparent than real by virtue of the fact that the red blood cells are seen to be tightly packed in clumps, which would effect a redistribution of the plasma to create columns of corpuscle-free fluid. This question must be investigated further.

Our electrophoretic studies revealed no change in plasma proteins during hypothermia, indicating that the observed hemoconcentration is due to sequestration or loss of whole plasma.

Our observation of intravascular agglutination of erythrocytes in the mesenteric vessels extends the observations of Bigelow, Lindsay, and Greenwood[2] and Gelin and Lofstrom[9] who noted this phenomenon in the conjunctival vessels of hypothermic dogs. Capillary blockage by agglutinated masses of erythrocytes was seen only in those of our dogs in which the agglutination was most severe.

SUMMARY AND CONCLUSION

Blood studies of dogs subjected to immersion hypothermia and permitted to warm at room temperature revealed the following changes. There was during hypothermia a prolongation of clotting time, a decrease in platelet thromboplastic factor consistent with a decrease in the number of circulating platelets and a decrease in prothrombin consumption, but essentially no change in prothrombin time or fibrinogen concentration. All recognized deviations during hypothermia returned toward or exceeded normal during the warming phase. The concentration of fibrinogen increased during the warming phase. The coagulation studies indicate that the prolonged clotting time during hypothermia is due to a reduction of platelets.

An increase in sedimentation rate and hematocrit reading was observed. Electrophoretic analysis of plasma from the hypothermic dog showed no consistent or significant change in total or relative concentration of proteins when compared with normal plasma.

A precipitous drop occurred in the total number of leukocytes with a return toward normal during the warming of the animal. Lymphocytes were the only cells to show a percentage increase during hypothermia, while the neutrophils and eosinophils showed a percentage decrease. During the warming phase eosinophils continued to drop while the other cells approached their control values. The erythrocyte fragility test did not show any change.

Mesenteric vessels observed during hypothermia revealed intravascular agglutination of erythrocytes, reduction of flow rate, apparent hemoconcentration, and sticking of white cells to venule walls.

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EPIDERMOID CYST OF THE SKULL

Report of Four Cases and Review of the Literature

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INTRODUCTION

An epidermoid tumor of the skull is an uncommon lesion usually seen by a radiologist or neurosurgeon. This report consists of a review of the literature and 4 additional case histories. Since the condition can be confused with more innocuous lesions of the scalp and skull, it was thought that a discussion presenting the major clinical features might be timely.

HISTORY

Cruveilhier[5] first described this condition in 1829, introducing the term "tumeurs perlees." Additional cases were presented by Muller[15] in 1838 as cholesteatomas, since he had found cholesterin crystals in some instances. Remak[18] identified the cellular origin of these growths as being ectodermal and adopted the term "epidermoid," the correctly accepted designation.

ETIOLOGY

The precise histogenesis of this tumor is not established although one theory is that they may arise from misplaced cells during embryogenesis which have epidermatogenic potentialities. Remak described these tumors as originating from epithelial cell rests, but the overshadowing influence of Virchow,[21] who felt that they were secondary to cellular metaplasia, temporarily blunted this concept. It remained for Bostroem[3] in 1897 to revive Remak's[18] theory. It has been suggested that with trauma, epithelial cells are driven deep within the scalp or bones of the cranium, giving rise to these lesions. However, Love and Kernohan[11] found apocrine glands in the wall of the cyst in an epidermoid of the scalp with a definite history of trauma. The presence of these highly specialized glands in this area, where they are never found, helps to confirm the misplaced cell rest theory rather than that of implantation by trauma. A history of associated trauma is, undoubtedly, coincidental rather than causative. A similar lesion is occasionally encountered in the distal phalanges of the hand and is thought to result from trauma. In this series, we found 9 cases with history of trauma and 25 without any injury of the skull.

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INCIDENCE

In a review of the literature, approximately 70 cases of intradiploic epidermoid cysts are reported. Mahoney[12] in 1936 reported one case and was able to collect 23 other cases. He did not include Bucy's,[4] Rosenwasser's,[19] and Love and Kernohan's[11] cases. Our review starts from 1936 and ends Dec. 31, 1955. We were able to collect 33 cases but studied only 30 of these plus our own 4 cases. From 1947 to 1955, 32,836 surgical admissions were recorded at Saint Joseph's Infirmary. Only 4 of these were reported as epidermoid cysts of the skull (Table I).

AGE AND SEX

This tumor has been reported to occur from infancy to 70 years of age with the average age being 32 years at the time of diagnosis. The sex distribution is about equal. The age and sex distribution are outlined in Table II.

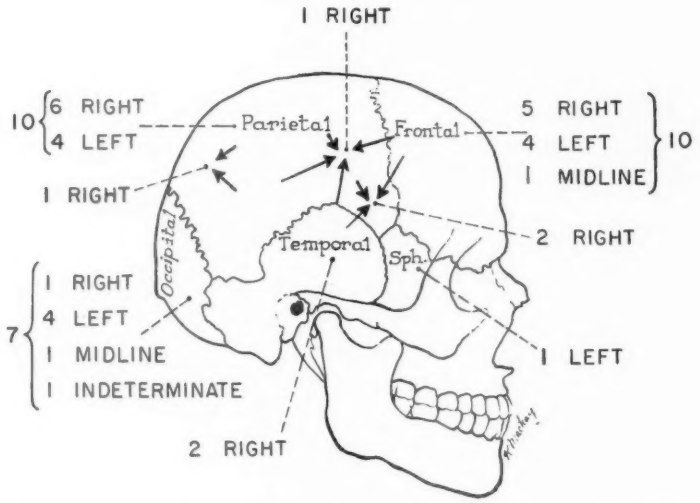

Fig. 1.—Location of 34 cases of epidermoid cysts of the skull.

PATHOLOGY

This lesion can be located in any part of the skull. In this series of 34 cases, 10 were located in the frontal bone, 10 in the parietal, 6 in the occipital, 2 in the temporal, and 1 in the sphenoid. In 15 cases, 2 or more subdivisions of the skull were involved by the cyst. Eighteen of the cases were located on the right and 13 on the left side. Two of them were midline (Fig. 1).

The cyst can involve the outer, inner, or both tables of the skull. In many instances, the dura is involved. In this series, both tables were involved in 46 per cent of patients, both tables and dura in 10 per cent, outer table in 31 per cent, inner table in 7 per cent, inner table and dura in 3 per cent, and inner table and dura plus compression of the brain in 3 per cent of cases (Fig. 2).

Grossly the lesion is a soft cystic structure with a thin grayish-white wall. The cyst contents appear pearly white and occasionally fine crystals are seen.

TABLE

CASE NO. AND AUTHOR	SEX	AGE AT EXAMINATION	AGE AT ONSET	REGION*	INJURY ?	SIZE	SYMPTOMS
1. Bucy 1935	M	28	5	R.-P.		1½ × 1¼ inches	Convulsions
2. Bucy 1935	F	26	24	L.-F.		1½ × 1½ inches	
3. Bucy 1935	M	39	Many years ago	Midline F.		2½ × 1½ inches	
4. Rosenwasser 1935	M	54	54	L.O.		Small egg	
5. Love and Kernohan 1936	F	43	10	R.P.	Yes	7½ × 5½ cm.	None
6. Love and Kernohan 1936	No case history, lack of space in abbreviated article in J. A. M. A.						
7. Love and Kernohan 1936	No case history, lack of space in abbreviated article in J. A. M. A.						
8. Geschikter 1936	No case history, author reports 15 cases—"cysts, cholesteatomas, Brodie's abscess"						
9. Graumann 1937	F	30	30	O.	Yes	8 cm. diam.	Headache
10. Monroe and Wegner 1937	F	37	10	R.T.	Yes		Headache
11. King† 1939	M	28	23	R.T. P.F.	Yes	2 × 2½ inches	Difficulty with left leg, dizziness, impaired vision
12. King 1939	M	27		L.F.		2 cm. diam.	None
13. King 1939	M	26	25	L.O.	No	2½ cm.	Headache
14. King 1939	M	46		R.F.		5 × 7 cm.	Pains right eye, headache
15. Rowbotham 1939	M	26	22½	L.F.		1¼ inch diam.	Creepy sensation and fainting attacks for past 2½ years
16. Rowbotham 1939	F	35	34½	L.O.			Convulsive seizure, headache, dizziness, vision failure, mental deterioration
17. Alpers 1939	F	52	40	R.O.	Yes	1 inch diam.	Visual disturbances, headache, and nausea
18. Quade and Craig 1939	F	23	21	L.P.		4 cm. diam.	
19. Love and Bailey 1940	M	46	32	L.O.			Headaches, pain over right eye with blurred vision and photophobia, lost consciousness and many other complaints

*Region: R., Right; L., Left; F., Frontal; T., Temporal; P., Parietal; O., Occipital; S., Sphenoid.
†In 1950 Dr. King reoperated upon one patient 11 years after original operation.

TABLE I

FINDINGS AT EXAMINATION	PREOPERATIVE DIAGNOSIS	FINDINGS AT OPERATION	RECURRENCES	OBSERVATION
Slight pulsation, bony ridge	Yes	Erosion outer table, broken inner table, enucleation with removal of inner table		
Local swelling with bony ridge		Erosion of both tables, partial removal	Yes	
Local swelling with raised bony margin		Erosion of both tables, removal		Cyst found connected by pedicle to another collection of cholesteatomous material within the skull
Tender painful mass	No	(1) Incision and drainage because of infection, (2) excision with curette 2 months after incision and drainage	No	
Bony defect, mass	Yes	Both tables destroyed, complete removal		
Swelling with bony defect, papilloedema right side, increased spinal pressure	No	Dura had no connection with tumor	No	
Swelling with irregular bony defect		Defect of inner table		
Hard swelling	Yes	Both tables destroyed, complete enucleation and resection of adherent dura	No	
Palpable mass	No	Destruction of outer and depression of inner table, complete extirpation	No	
Firm elevation fixed to skull, larger left pupil	Yes	Both tables destroyed, incomplete removal, curettage	No	
Palpable tumor with erosion of upper orbit rim	No	Both tables destroyed, depression of dura, removal by scraping and scooping	No	5 years ago right eye enucleated for suspected tumor, no tumor found, x-ray shows marked destruction of lesser and some of greater wing sphenoid bone
Painless swelling		Outer table disappeared, curettage		
No visible or palpable swelling in the skull		Both tables destroyed, tumor was resting on dura, all traces of tumor capsule removed		Neurologic findings were due to diffuse astrocytoma in right lobe of brain (2 entirely separate conditions)
"Soft spot" with bony destruction	No	Bulging of inner table, erosion and compression of brain, removed completely		Case has been reported previously by Alpers and Harrow in 1932
Soft, tender, fluctuant swelling		Lying on the dura, complete removal		Diagnosis of wen made and excision attempted but wound did not heal
Complete anosmia, slight nerve deafness on both sides	Yes	L.O. lobe pushed over and left lobe of cerebellum displaced, complete removal		Father died of brain tumor of unknown nature

CASE NO. AND AUTHOR	SEX	AGE AT EXAMINATION	AGE AT ONSET	REGION*	INJURY ?	SIZE	SYMPTOMS
20. May et al. 1942	M	60	54	R.F.-T.-P		10 × 5 cm.	
21. Rand and Reeves 1943	M	13	10	R.F.		2 cm. diam.	Headache and vomiting after he struck head and ruptured cyst
22. Rand and Reeves 1943	F	23	18	L.O.	Yes	2½ × 3½ cm.	Headache and ringing in ears
23. Rand and Reeves 1943	F	18	13	L.P.		3 × 2 cm.	
24. Rand and Reeves 1943	F	44	8	R.F.		6 cm. diam.	
25. Rand and Reeves 1943	F	54		R.T.		4½ × 3½ cm.	Convulsive seizures,
26. Rand and Reeves 1943	M	32	32	Mid-O.		7 × 6 × 2½ cm.	Eyes tired easily, dizziness
27. Rand and Reeves 1943	M	64	9	L.P.		10 × 8 cm.	
28. Rand and Reeves 1943	F	65	51	L.F.	Yes	4 × 5 × 1 cm.	Convulsions, headaches
29. Rand and Reeves 1943	M	21		R.P.	Yes		Headache, vomiting
30. King 1948	M	54	44	R.F.-P.-T.-O	Yes	10 cm. diam.	Difficulty with left leg
31. King 1948	F	46	46	R.T.-P.			None
32. Adelstein 1949	F	14	7	R.F.	Yes	2 × 3 cm.	Headaches
33. Adelstein	F	27	20	R.P.	No	5 cm. diam.	Headaches
34. Skandalakis, Godwin, Mabon 1956	F	22 months	2 months	R.F.	None	1 cm. diam.	None
35. Skandalakis, Godwin, Mabon 1956	M	3½	3½	L.S. lesser wing	None	1½ cm. diam.	None
36. Skandalakis, Godwin, Mabon 1956	F	13	12	R.P. post.	None	7 × 3½ cm.	None
37. Skandalakis, Godwin, Mabon 1956	M	13	Several years ago	R.P.	None	2½ cm. diam.	None

TABLE I—CONT'D

FINDINGS AT EXAMINATION	PREOPERATIVE DIAGNOSIS	FINDINGS AT OPERATION	RECURRENCES	OBSERVATION
	No			5 years P.T.A.* The Schüller-Christian disease diagnosed, same diagnosis this admission, at autopsy epidermoid cyst found, it is not certain this case presents intradiploic-epidermoid or is secondary to chronic inflammation of ear because cyst perforated to the middle ear
Kerning and Babinski signs were present bilaterally	Yes	Both tables destroyed	Yes	Operated on first for supposed sebaceous cyst, found cyst extended through the inner table
Large mass	Yes	Outer table destroyed		
	Yes	Outer table destroyed, enucleation and curettage	Yes	Patient operated on (4 times) for a supposed sebaceous cyst
Cystic mass	No	Outer table destroyed, (1) removal of contents, (2) inner table intact, removal of tumor and sac	Yes	(2 times) between first and second operation many aspirations of tumor were done
	Yes	Between inner table and the dura, incomplete removal		
Hard and soft swelling, bilateral papilloedema		Both tables destroyed, incomplete removal		
Entire left side of scalp was boggy	?	Outer table destroyed	Yes	Repeated operations at 34, 36, and 44 years of age, continued drainage, at age of 64 new operation, since then 2 operations, died from bronchopneumonia at 66 years, squamous cell carcinoma-section through parietal region
Swelling	Yes	Outer table intact, inner table eroded, incomplete removal		
Depression in the skull admitting a fingertip	Yes	Dumbbell-shaped cyst, both tables destroyed, complete removal with dura		
Large mass	Yes	Both tables destroyed, dura involved, resection of dura with fascia lata graft	No	
Slight elevated mass, slight increase in deep reflexes on left side	Yes	Both tables destroyed, dura involved, resection of dura with fascia lata graft	No	Lesion discovered incidentally by x-rays
Firm and craterlike edges		Both tables destroyed, removal in toto	Yes	One was found on second operation, pericranium and tumor mass removed
Soft painless mass	?	Both tables destroyed, dura involved, curettage	No	
Firm mass	Yes	Outer table destroyed, complete removal	No	
	Yes	Outer table destroyed complete removal	No	Lesion discovered incidentally by x-rays
Painless, soft, fluctuant mass	Yes	Outer table destroyed, inner table irregular, complete removal	No	
Firm mass	Yes	Both tables destroyed, complete removal	One 6 years after first operation	Complete removal on second operation

*P.T.A. = Prior to admission.

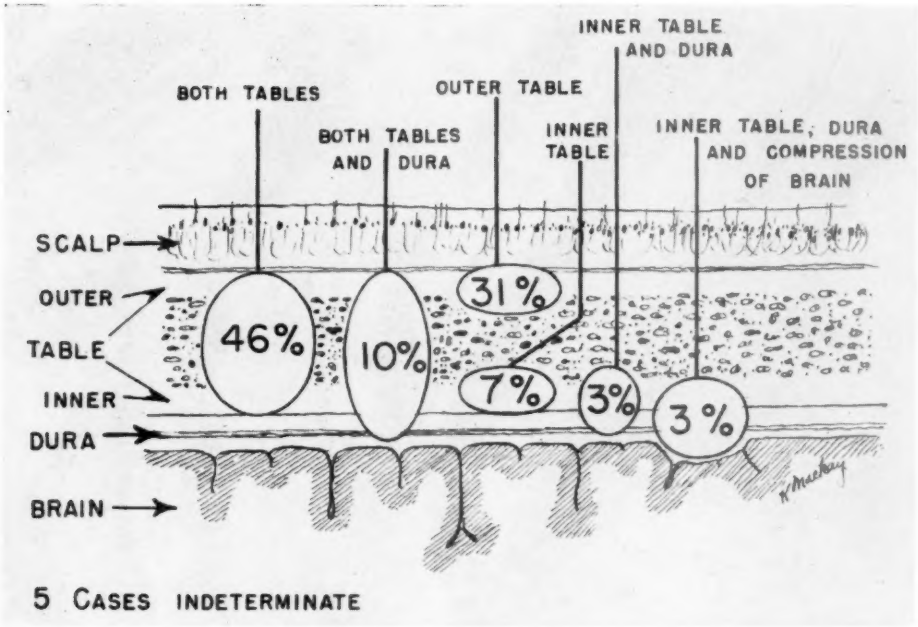

Fig. 2.—Local pathologic findings in 29 cases.

Fig. 3.—Epidermoid cyst showing stratified squamous epithelium and desquamated keratinized cells within cavity. (Hematoxylin and eosin, ×140.)

TABLE II. AGE AND SEX DISTRIBUTION IN 34 CASES

AGE AT TIME OF EXAMINATION	SEX		TOTAL
	MALE	FEMALE	
1-10	1	1	2
11-20	2	3	5
21-30	6	5	11
31-40	2	2	4
41-50	1	4	5
51-60	3	2	5
61-70	1	1	2
Total	16	18	34

Microscopically the cyst wall is composed of dense fibrous tissue lined by stratified squamous epithelium. The contents are keratinized squamous epithelial cells. Occasionally cholesterol crystals are present (Fig. 3). Usually no skin appendages such as sweat glands are demonstrated. Histologically the lesion is identical to epidermal cysts and the epidermoid cysts of the distal phalanges of the hands.

SYMPTOMS AND SIGNS

This tumor can be asymptomatic and may vary considerably in size. It may be present at birth but may be noted at any age and is sometimes incidentally found upon examination for other reasons. The lesion may be mistaken for a cutaneous epidermal or sebaceous cyst. Roentgen examination of the skull will differentiate the two. Even if erosion of the outer table has occurred, the mass is usually soft and painless to palpation. It may be present for many years before manifesting symptoms. In this series 15 cases (44 per cent) were asymptomatic and 19 (56 per cent) presented symptoms as shown in Table III.

TABLE III. SYMPTOMS IN 34 CASES

Without symptoms		15 (44%)
With symptoms		19 (56%)
Headache	4	
Nausea	1	
Vomiting	3	
Dizziness	3	
Ringing in the ears	1	
Convulsions	4	
Fainting attacks	2	
Visual disturbances	6	
Difficulty in using leg	1	
Total		34 (100%)

Table IV correlates the symptoms with the operative findings in 34 cases. In 5 cases with dura involvement, 4 had neurologic findings. In 25 cases in which the dura was not involved, neurologic signs and symptoms were found in 13.

It is very difficult to explain the presence of neurologic deficit in cases in which the dura was not involved. In some instances, more than one symptom

TABLE IV. FINDINGS AT OPERATION IN RELATION TO SYMPTOMS IN 34 CASES

PART INVOLVED	WITH SYMPTOMS	WITHOUT SYMPTOMS	TOTAL
Outer table	2	7	9
Inner table	2	0	2
Both tables	9	4	13
Inner table and dura	1	0	1
Both tables and dura	2	1	3
Inner table, dura and compression of brain	1	0	1
Both tables, dura and compression of brain	0	0	0
Indeterminate	2	3	5
Total	19	15	34

was present. In the second case of Rowbotham,[20] the neurologic findings were due to a diffuse astrocytoma of the right temporal lobe. Logically, the lesions should be totally asymptomatic when involving the skull only.

ROENTGENOLOGY

Roentgen examination of the calvarium is essential for a correct preoperative diagnosis. Usually there is erosion of the outer and occasionally of the inner table of the skull. The eroded edges are commonly dense, producing a craterlike appearance. This was accentuated by stereoscopic examination. If completely intradiploic the inner and outer tables may be expanded with a central radiolucent area (Figs. 4, 5, 6, 7).

TREATMENT

Complete surgical extirpation is the recommended treatment. If the lining is not completely removed or destroyed it may continue to grow and form a new cyst.

In 6 of 34 cases of epidermoid cysts of the skull, there were 15 recurrences (Table V). In other words, 28 cases were free of recurrence from 1 to 20 years after surgery. Four cases were on the right side and 2 on the left side of the skull. All recurrences happened in individuals in which the tumor was located

TABLE V. 15 RECURRENCES IN 6 OF THE 34 CASES OF EPIDERMOID CYSTS OF THE SKULL

CASES	BONE	NUMBER OF RECURRENCES		INVOLVED AREA	OPERATION
		RIGHT SIDE	LEFT SIDE		
1	Frontal	1		Both tables	?
2	Parietal		4	Outer table	Enucleation and curettage
3	Frontal	2		Outer table	Removal of tumor and sac
*4	Parietal		6	Outer table	Repeated removals
5	Frontal	1		Both tables	Removal in toto
6	Parietal	1		Both tables	Complete removal
	Subtotals	5 +	10		
	Total	15			

*Died from bronchopneumonia. Squamous cell carcinoma on sections through the parietal region.

Fig. 4.—X-ray of skull in Case 1 (No. 34 in Table I) showing bony defect on the right frontal bone.

Fig. 5.—X-ray of skull in Case 2 (No. 35 in Table I) showing bony defect on the lesser wing of the left sphenoid bone.

in the frontal or parietal bones. In 3 cases the outer table was involved and in the other 3 cases both tables were found involved. In 2 instances there were 10 recurrences. In the first patient, the cyst was excised 4 times and in the second, 6 times. In this latter instance, the patient succumbed to bronchopneumonia. On autopsy, a squamous cell carcinoma was found in sections of the parietal region.

Fig. 6.

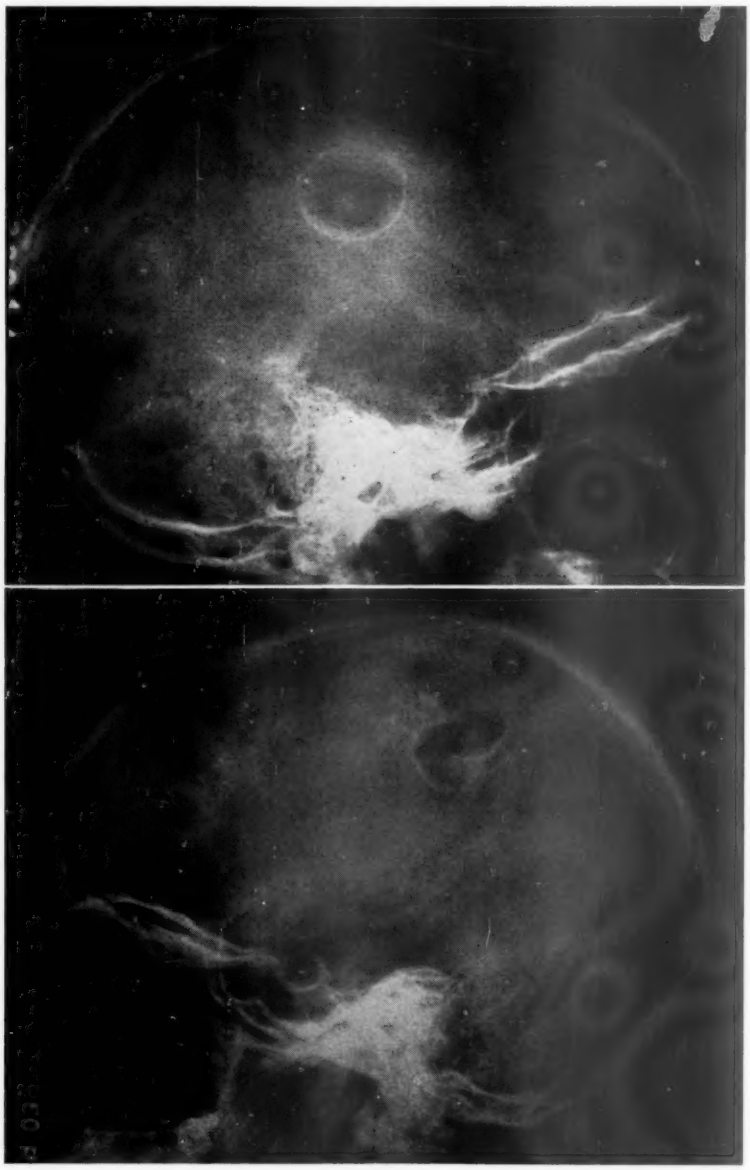

Fig 7.

Fig. 6.—Case 3 (No. 36 in Table I) showing bony defect on the right parietal region posteriorly.

Fig. 7.—Case 3 (No. 37 in Table I) showing bony defect on the right parietal region. Note the abnormality of the defect due to a previous operation.

SUMMARY

Thirty-four cases of intradiploic epidermoid cysts of the skull have been reviewed, including 30 examples collected from the literature during the period 1936 through 1955, with 4 examples of our own. This condition is relatively uncommon, but should always be suspected in a palpably cystic lesion of the scalp, no matter how benign it may appear. X-rays of the skull prove invaluable in determining bony involvement in what seems to be an innocuous cutaneous cyst, leading to the correct diagnosis.

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Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

THE SURGICAL TREATMENT OF METASTATIC PULMONARY LESIONS

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THE earliest data regarding respective procedures for metastatic cancer of the lung consisted for the most part of isolated case reports. These along with subsequent collected series (Alexander and Haight[1] and Effler and Blades[4]) have been listed and reviewed in detail by Seiler, Clagett, and McDonald,[11] who reported a 37 per cent salvage in 62 patients, this number including 10 cases of their own.

Since that report their series increased to 43, which included patients treated prior to 1952, and of this group a 33 per cent 3-year survival was accomplished.[7]

Other published series (Ehrenhaft[5] with a salvage of 7 out of 9 patients over a short follow-up period, Higginson[6] with a 50 per cent survival in 22 cases resected followed from one month to over 6 years, Kelly and Langston[8] reporting 5 patients alive of 18 in their series, and Strieder[12] with 10 patients alive of 20 operated upon) demonstrate quite definitely the value of this type of therapy when one is faced with a seemingly hopeless problem. It is true that optimism may be premature since follow-up is not for a 5-year period, although in the last-mentioned group 7 of the 10 had been followed for over 3 years.

Kergin,[9] however, points out that there may be erroneous conclusions drawn from reporting just successful cases and urges the reporting of poor as well as good results to allow for more accuracy in evaluating this surgical measure.

MATERIAL AND ANALYSIS

Our material consists of 50 patients treated from 1941 through 1957; April, 1958, was the last date of follow-up for survival time. The patients have been grouped according to primary sites or types in the following tables and short abstracts of the longer-term survivors from these have been included.

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Malignant Kidney Lesion.—The first group which has been considered is that of the malignant kidney lesion. Our efforts in this group have been a complete failure, with no patient living more than one year and 3 months.

This failure is in contrast to the consensus of favorable prognosis afforded by this lesion as shown in the remarkable case of Barney and Churchill,[2] 2 cases of Strieder[12] 4½ and over 8 years, respectively, and the almost 8-year survival as reported by Hood, McBurney, and Clagett.[7] Unfortunately, in our group 2 patients expired in the postoperative periods and this immediately eliminated one-third of the number. In the first patient no attempt was made to remove the renal lesion because the pulmonary resection did not accomplish complete excision of the metastatic process. The child (Case 5) was stricken with an embryonal type of kidney tumor which, prior to death, demonstrated further dissemination in spite of all therapy. The patient in Case 2 developed and had surgical therapy for 2 distinct primary lesions (breast and kidney) within 6 months. At autopsy metastasis was found completely replacing the right adrenal gland and histologically was characteristic of the original primary renal lesion. No other metastases were found and death was attributed to pulmonary edema and hyperemia secondary to cardiac failure.

Breast Carcinoma.—Table II includes patients with history of breast carcinoma preceding pulmonary resection and this primary site provided the largest number of cases.

Of these resected cases, 4 are living; 3 are entirely free of disease after 4 years, 11 months, and 8 months, respectively. The patient with disease actually had a pleuropneumonectomy, but all thoracic tumor was not removed and she underwent hypophysectomy in February, 1957, with apparent control of the neoplasm.

This group provided exceptional interest in reviewing the histologic material, which was obtained in the majority of cases. In 3 of the cases with material studied from both sites (breast and lung), we noted the distinct tendency of the pulmonary lesion to resemble a squamous tumor. Case 11 is one in point. Studies of the resected lobe for a 5 to 6 cm. solitary mass were first considered as primary bronchogenic disease until a review of the initial breast lesion 2 years earlier demonstrated identical squamous metaplasia. In both surgical procedures (done at Research and Educational Hospitals), the axillary and hilar glands were without demonstrable disease.

Case 9 had an interpretation of carcinoma simplex made on review of the breast slide. Because the lung lesion was entirely at the hilus and the bronchial wall showed changes suggesting a primary lesion, this was initially considered as a second primary tumor. A large subcutaneous lesion removed 9 months after pneumonectomy demonstrated characteristics suggesting the breast primary. Confronted with all the histologic material one pathologist admitted the impossibility of stating whether the process represented one or 2 separate tumor entities from purely the morphologic standpoint.

Further, in 3 of these women in whom the microscopic features suggested squamous origin, a history of smoking was never obtained.

TABLE I. KIDNEY

PATIENT	AGE	SEX	TYPE	SURGERY I	DATE	INTERVAL	DATE	PULMONARY SURGERY	STATUS
1. R. C.	58	M	Hypernephroma	No renal surgery	—	—	3-50	Right lung	Dead—1 yr. 3 mo.
2. V. J.	59	F	Hypernephroma, adenocarcinoma	Left nephrectomy, right mastectomy	6-48 12-48	1 yr. 5 mo.	11-50	Right lung	Dead—postoperative
3. H. McM.	59	M	Hypernephroma	Right nephrectomy	1940	11 yr.	11-51	Right lung	Dead—1 yr.
4. H. W.	48	F	Hypernephroma	Right nephrectomy	6-44	7 yr. 10 mo.	4-52	Left lung	Dead—postoperative
5. D. D.	3½	F	Wilms	Left nephrectomy	7-51	2 yr. 3 mo.	10-53	Left upper lobe	Dead—1 yr. 1 mo.
6. R. S.	45	M	**Transitional cell**	Left nephrectomy	8-53	1 yr. 6 mo.	2-55	Left lower lobe	Dead—6 mo.

TABLE II. BREAST

PATIENT	AGE	SEX	TYPE	TREATMENT	DATE	INTERVAL	DATE	PULMONARY SURGERY	STATUS
1. L. H.	29	F	Carcinoma	Right radical	6-45	4 yr. 11 mo.	5-50	Left upper lobe	Dead
2. A. B.	50	F	Adenocarcinoma	Right radical	7-52	11 mo.	6-53	Segment right upper lobe and chest wall	Dead—3 mo.
3. B. B.	57	F	Adenocarcinoma	Left radical	8-51	1 yr. 10 mo. 2 yr. 11 mo.	6-53 7-54	Lingula; right upper lobe, 2 subsegments	Dead—10 mo.
4. T. K.	63	F	Carcinoma simplex	Right radical	-49	5 yr.	4-54	Right lung	Living and well—4 yr.
5. A. S.	59	F	Adenocarcinoma	Right radical	3-50	5 yr. 3 mo.	6-55	Left lung	Dead—1 yr. 3 mo.
6. L. T.	66	F	Adenocarcinoma	Left radical	-52	4 yr.	3-56 9-56	Left upper lobe Left lower lobe	Dead—postoperative
7. F. M.	40	F	Adenocarcinoma	Left radical	-52	4 yr.	8-56	Right lung and pleura (hypophysectomy, 2-57)	Living—with tumor 1 yr. 8 mo.
8. L. L.	66	F	Medullary duct carcinoma	Right radical	10-52	4 yr.	10-56	Left upper lobe	Dead—1 yr. 3 mo.
9. R. B.	66	F	Carcinoma simplex	Left radical	12-53	2 yr. 10 mo.	10-56	Left lung	Dead—1 yr. 1 mo.
10. M. K.	73	F	Adenocarcinoma	Left radical	5-47	10 yr.	5-57	Left upper lobe, posterior apical and anterior segment	Living and well—11 mo.
11. G. Y.	57	F	Carcinoma with squamous metaplasia	Right radical	8-55	2 yr.	8-57	Right lower lobe	Living and well—8 mo.

We would think that, as a general rule, one should consider patients developing pulmonary neoplasms after a history of breast carcinoma as having metastatic rather than secondary primary carcinoma. This is in exception to cases in a published series by Cahan and associates.[3]

Adenocarcinoma of Colon.—The colon group comprised 8 cases and these are tabulated in Table III.

As will be noted, 4 patients are alive and well followed for periods of 6 years, 2 years, 1 year and 3 months, and 5 months, respectively. A brief abstract of the history of the 6-year survival follows.

Case 3 (Colon Series).—The patient (G. H.), a 53-year-old Negro woman, was admitted to St. Luke's Hospital on Jan. 3, 1947, with a history of bleeding from the rectum for 9 months. During the past 7 months, there had been alternating constipation and diarrhea, and in this period her weight had decreased by 15 pounds.

On physical examination, temperature, pulse, and respirations were normal and blood pressure 130/80. The head, neck, and chest were essentially negative, but tenderness was elicited on deep palpation in the left lower quadrant of the abdomen. No masses were palpable, however, and rectal examination was negative.

Laboratory findings revealed a red blood cell count of 2.8 million, a hemoglobin of 7.0 Gm., and a white blood cell count of 9,300. Serology and urine were negative and blood chemistry was essentially within normal limits.

A barium enema (Fig. 1) was diagnostic of a sigmoid lesion with partial obstruction.

Fig. 1.—Barium enema; obstructing lesion in sigmoid loop.

After transfusion and sulfonamide bowel preparation, an anterior resection and anastomosis were performed on Jan. 11, 1947 (Dr. B. Kilbourne). No mesenteric nodes or liver metastases were found and no positive nodes were identified in the surgical specimen. The patient's convalescence was uneventful and she was discharged from the hospital.

The second admission occurred on March 18, 1952. Her complaints at that time were cough of 4 to 5 months' duration, slight hemoptysis, and slight shortness of breath. She had lost 4 pounds in the past month. Chest x-rays taken in January and April of 1952 demonstrate the progression of the lesion seen on both posteroanterior and lateral views (Fig. 2, *A* and *B*).

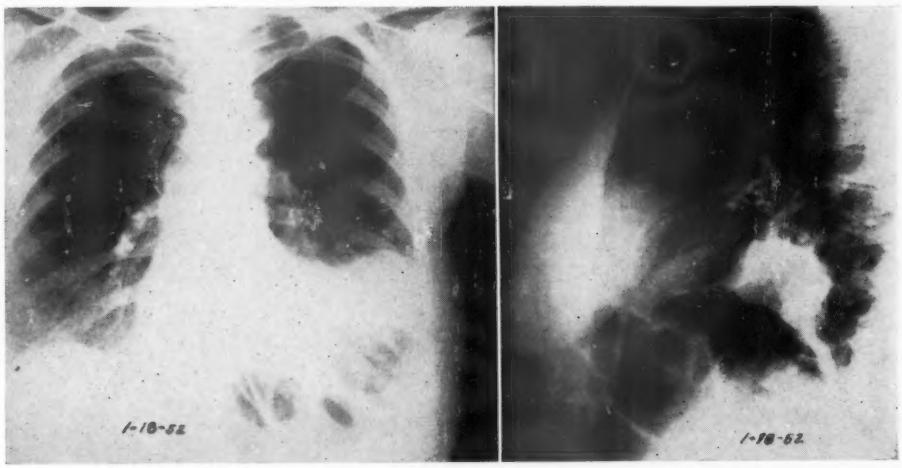
At this admission temperature was 100, pulse 110, and respirations 26. Physical findings were limited to the left base where dullness and diminished breath sounds were the significant changes.

TABLE III. ADENOCARCINOMA OF THE COLON

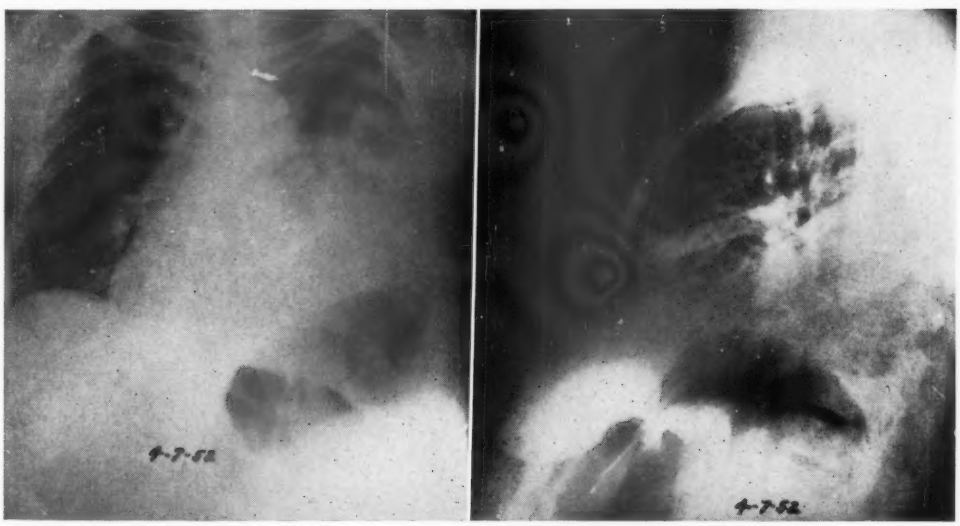
PATIENT	AGE	SEX	PRIMARY SITE	SURGERY I	DATE	INTERVAL	DATE	PULMONARY SURGERY	STATUS
			Colon						
1. L. H.	42	F	Polyposis	Abdominoperineal; coloctomy	5-41 1-44	4 yr. 6 mo.	11-45	Right lower lobe	Dead—6 mo.
2. P. W.	52	F	Sigmoid	Anterior resection; cecostomy	3-46	3 yr 3 mo.	7-49	Right lower lobe	Dead—9 mo.
3. G. H.	53	F	Sigmoid	Anterior resection	1-47	5 yr. 3 mo.	4-52	Left lung	Living and well—6 yr.
4. R. C.	57	F	Sigmoid	Anterior resection	8-47	7 yr. 3 mo.	11-54	Right lung	Dead—2 yr. 1 mo.
5. A. G.	57	F	Sigmoid	Resection and exterior anastomosis	11-54 2-55	1 yr. 5 mo.	4-56	Right lung	Living and well—2 yr.
6. A. C.	56	M	Rectum	Abdominoperineal	7-54	2 yr. 1 mo.	8-56 11-56	Subsegment upper and lower lobes; anterior medial left lobe; lingula, upper lobe	Dead—1 yr. 5 mo.
7. M. F.	68	F		Resection and anastomosis	1-54	3 yr.	1-57	Left lower lobe	Living and well—1 yr. 3 mo.
8. A. G.	65	F	Rectum	Abdominoperineal	3-53	4 yr. 5 mo.	11-57	Left lung	Living and well—5 mo.

Laboratory findings revealed a red cell count of 3.7 million, white cell count of 12,800, and hemoglobin 11.8 Gm.

Proctoscopic examination and barium studies demonstrated no evidence of obstruction. Bronchoscopy by the Holinger and Johnston service revealed granular tissue in the left lower lobe from which area tissue revealed metastatic carcinoma of the colon (Fig. 3, *A*).



A.



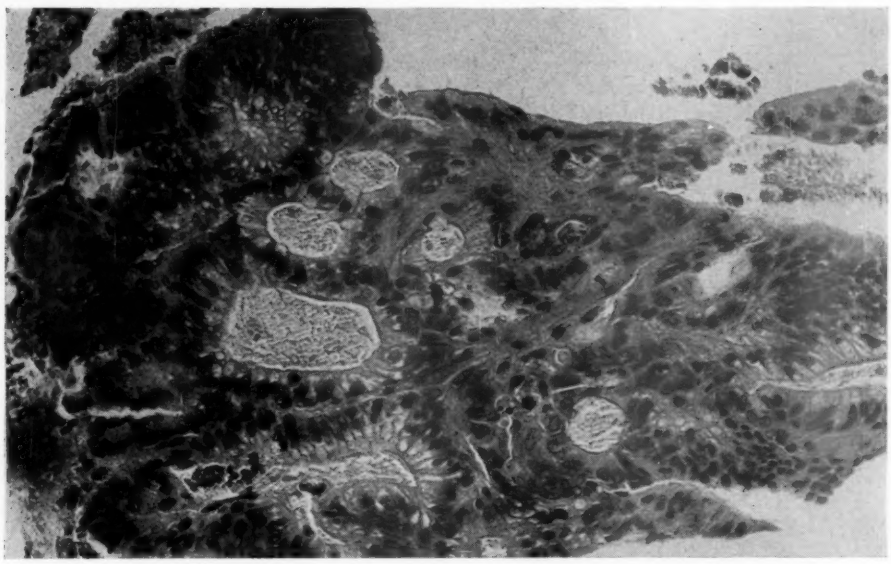
B.

Fig. 2.—Posteroanterior (*A*) and lateral (*B*) projections of chest as dated, demonstrating the increased involvement in the left lung field.

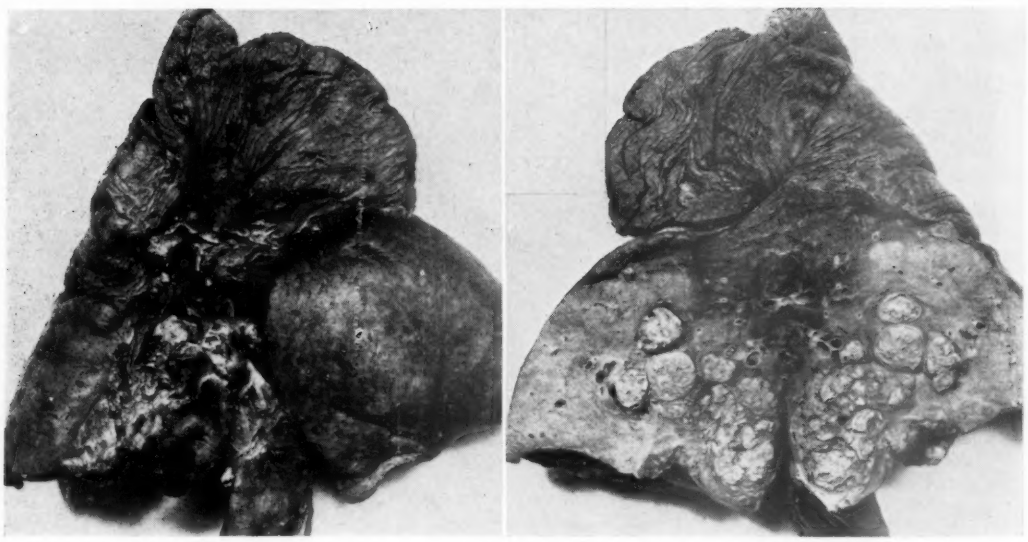
On April 9, 1952, a left thoracotomy was performed, revealing a completely consolidated left lower lobe with extensive inflammatory reaction at the diaphragm and along the pericardium. This accounted for the elevated diaphragm as seen on the chest x-rays. The left lung was removed and the patient was discharged after an uneventful convalescence. (Fig. 3, *B* and *C*.) The last follow-up x-ray (Fig. 4) demonstrates the chest status as of March, 1958. The patient is well without evidence of recurrence in abdomen, chest, or distant sites.

The 2 longest survivors appear to have significant survival times as practically all deaths occurred within 2 years following pulmonary resection in the reported cases, although in Strieder's series[12] one recurrence developed after 4 years, but the patient was alive with disease almost 7 years following the first thoracotomy.

There appears to be significant merit in this group.



A.



B. *C.*

Fig. 3.—*A*, Specimen reveals nodular intrabronchial tumor mass. *B*, Cut surface of lower lobe demonstrates globular masses of carcinoma with surrounding peripheral pneumonia. *C*, Positive bronchoscopic biopsy for metastatic colon carcinoma.

Tumors Developing in Female Genitalia.—Another rather favorable group is that of tumors developing in the female genitalia. These consisted of 5 epithelial and 2 mesothelial lesions as listed in Table IV.

In this group the 2 postoperative deaths reduced the follow-up number to 5; and, since 4 of these have survival periods of 6 years 9 months, 4 years 10 months, 2 years 2 months, and 2 years, respectively, this would suggest a much better outlook than might be expected from metastatic lesions as a group. The degree of malignancy of the first 2 are relatively low-grade and it is likely that this factor plays a significant part. On the other hand, the death in Case 4 was due to emboli breaking loose from tumor extending into the left atrium through the lumen of the superior pulmonary vein. It had enlarged and could not be withdrawn from the atrium, and a fair-sized portion was left attached to the endocardium.

The somewhat favorable outlook in this group is also substantiated in the Mayo series[7] as well as that of Strieder.[12]

Fig. 4.—Pronounced diaphragmatic elevation and tracheal shift in 6-year follow-up x-ray.

Miscellaneous Sarcoma.—The largest group is presented in Table V.

As will be seen, this group contains a wide variety of mesothelial lesions. Eliminating the one patient who was inoperable, only 3 of the 13 patients are alive, one only 5 months. Case 2 survived 9 years, however, but within 2 years following pulmonary resection recurring lesions appeared and over the next 7 years a series of local resections were performed for lesions on the trunk and extremities.

The most recent resection, Case 14, has a very grave prognosis since several lesions were found at thoracotomy, varying from a few millimeters to 2 cm. in size.

Practically speaking, we can expect a survival of 2 of 14, which is low and is not in keeping with the expressed generalization of Kergin.[9] His conclusion, however, is likely based upon the many isolated cases of small group reports in which only the good results were published. We have included all cases treated in this report, which allows for a more accurate appraisal.

An example of this is seen in Cases 1 and 4. The first represents a survival of 17 years 2 months following lobectomy and 29 years and 1 month following his first operation, a mid-thigh amputation of the left lower extremity.

TABLE IV. FEMALE GENITALIA

PATIENT	AGE	PRIMARY SITE	TYPE	TREATMENT	DATE	INTERVAL	DATE	PULMONARY SURGERY	STATUS
1. R. Z.	42	Ovary	Cyst-adeno(?)	Hysterectomy-oophorectomy	6-49	2 yr.	7-51	Right lung	Living and well—6 yr. 9 mo.
2. E. B.	46	Corpus uterus	Leiomyosarcoma	Hysterectomy	1942	11 yr.	6-53 3-54	Median lobe and subsegment	Living—4 yr. 10 mo. (1 node, left lung)
3. L. L.	55	Cervix uteri	Squamous carcinoma	Irradiation exenteration	2-50 5-54	5 mo.	9-54	Left lung	Dead—13 mo.
4. O. O.	51	Uterus and vagina	Sarcoma	Irradiation	1949 1951	6 yr.	11-55	Left upper lobe	Dead—postoperative
5. E. R.	58	Cervix uteri	Squamous carcinoma	Irradiation	6-53	2 yr. 8 mo.	2-56	Left lung	Living and well—2 yr. 2 mo.
6. G. N.	62	Corpus uteri	Adenocarcinoma	Irradiation; Wertheim	9-48	7 yr. 7 mo.	4-56	Right lung	Living and well—24 mo.
7. G. P.	64	Ovary	Papillary carcinoma	Hysterectomy-oophorectomy			10-56	Right lung	Dead—postoperative

TABLE V. MISCELLANEOUS SARCOMA

PATIENT	AGE	SEX	SITE	TYPE	TREATMENT	DATE	INTERVAL	DATE	PULMONARY SURGERY	STATUS
1. H. R.	27	M	Left femur	Osteogenic sarcoma	Mid-thigh amputation	2-29	12 yr.	2-41	Left upper lobe	Living and well —17 yr. 2 mo.
2. V. K.	33	F	Pleura, right lung	Fibroma (?)	Amputation	1938	4 yr.	1942	Right lung	Dead—9 yr.
3. A. S.	58	M	Right thigh	Fibro-sarcoma	Mid-thigh amputation	5-37	6 yr. 10 mo.	3-46	Left lower lobe	Dead—5 mo.
4. H. H.	36	F	Right elbow	Spindle cell	Local resection	1939-1942	5 yr.	2-47	Left upper lobe	Living and well —11 yr. 2 mo.
5. E. P.	48	F	Right axilla	Neurofibro-sarcoma	Local and radical excision	5-44 10-47		10-47	Right lower lobe	Dead—9 mo.
6. V. D.	23	F	Left femur	Osteogenic sarcoma	Mid-thigh amputation	3-48	1 yr. 1 mo.	3-49	Right lower lobe	Dead—13 mo.
7. F. S.	55	M	Posterior chest wall	Rhabdomyo-sarcoma	Radical excision	7-48	1 yr. 1 mo.	8-49	Left upper lobe	Dead—10 mo.
8. A. M.	45	F	Third finger, left hand	Fibro-sarcoma	Amputation	10-46	3 yr. 7 mo.	5-50	Inoperable	Dead—4 mo.
9. A. W.	34	M	Left leg	Spindle cell	Supracondylar	6-50	1 mo.	7-50	Lingula	Dead—1 yr. 3 mo.
10. A. G.	21	F	Right thigh	Fibro-sarcoma	Radical excision	3-49	14 yr. 8 mo.	11-50	Right upper lobe	Dead—1 yr.
11. M. W.	12	F	Left tibia	Osteogenic sarcoma	Below knee amputation	11-51	1 yr. 4 mo.	3-53	Right lung	Dead—1 yr. 2 mo.
12. A. K.	62	F	Right posterior mediastinum	Neurofibro-sarcoma	Resection of tumor	3-6-53	1 wk.	3-12-53	Right lung	Dead—1 yr. 9 mo.
13. M. J.	61	F	Left wrist	Neurofibro-sarcoma	Resection; irradiation	11-47 3-48 11-48	5 yr. 8 mo.	7-54	Left lung	Dead—5 mo.
14. D. T.	15	F	Left groin	Synovial sarcoma	Hemipelvectomy	1-57	10 mo.	11-57	3 subsegments right lung	Living and well 5 mo.

Case 1 (miscellaneous sarcoma series): This patient (H. R.), a 15-year-old white boy, entered St. Luke's Hospital on the orthopedic service of Dr. Ryerson on March 15, 1929. While skating in February, he injured his left lower thigh when he fell. In a short period of time the area just above the knee became swollen to one and one-half times normal.

Physical examination was negative except for the left lower extremity where the lower thigh was enlarged, slightly tender, and firm. X-rays of the femur demonstrated

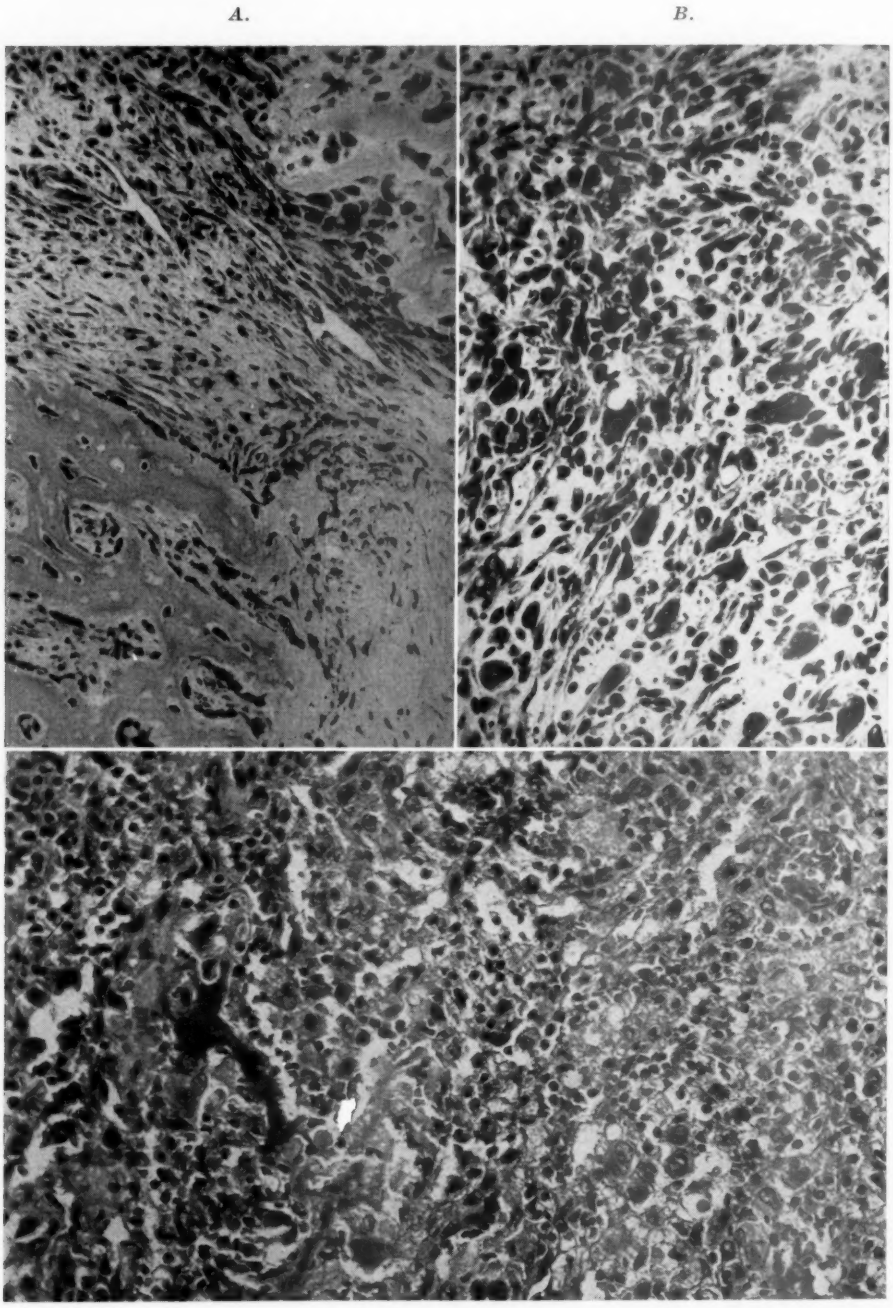
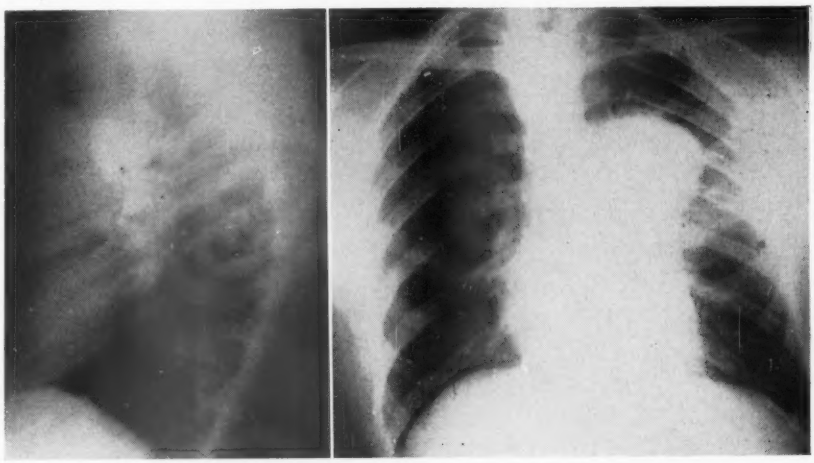
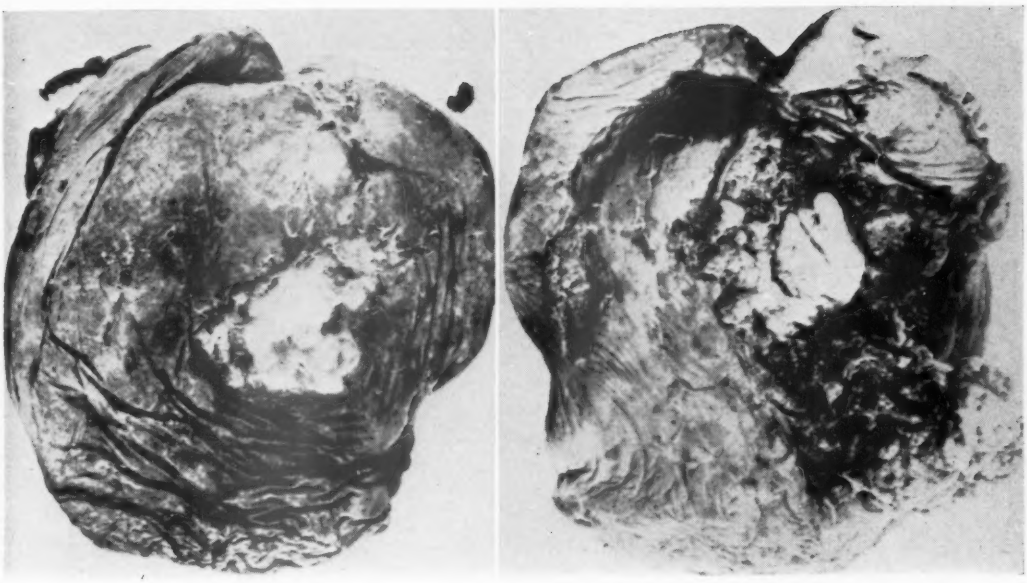


Fig. 5.—*A*, Low-power view of osteoid, fibrous, and hyaline tissues (specimen from femur). *B*, Higher power view of spindle, polyhedral, and giant cell elements (specimen from femur). *C*, Lung metastasis, bone formation on left.

changes interpreted as very likely sarcomatous in nature. A biopsy of this area was reported as osteogenic sarcoma and on March 19, 1929, a left mid-thigh amputation was accomplished (Fig. 5, *A* and *B*). The convalescence was somewhat prolonged and the patient was hospitalized for approximately 2 months following surgery.



A.



B. *C.*

Fig. 6.—*A*, Lateral and posteroanterior chest roentgenograms which reveal large hilar tumor mass. Views of upper lobe, which show cut surface of tumor (*B*), and the extension into lung parenchyma (*C*).

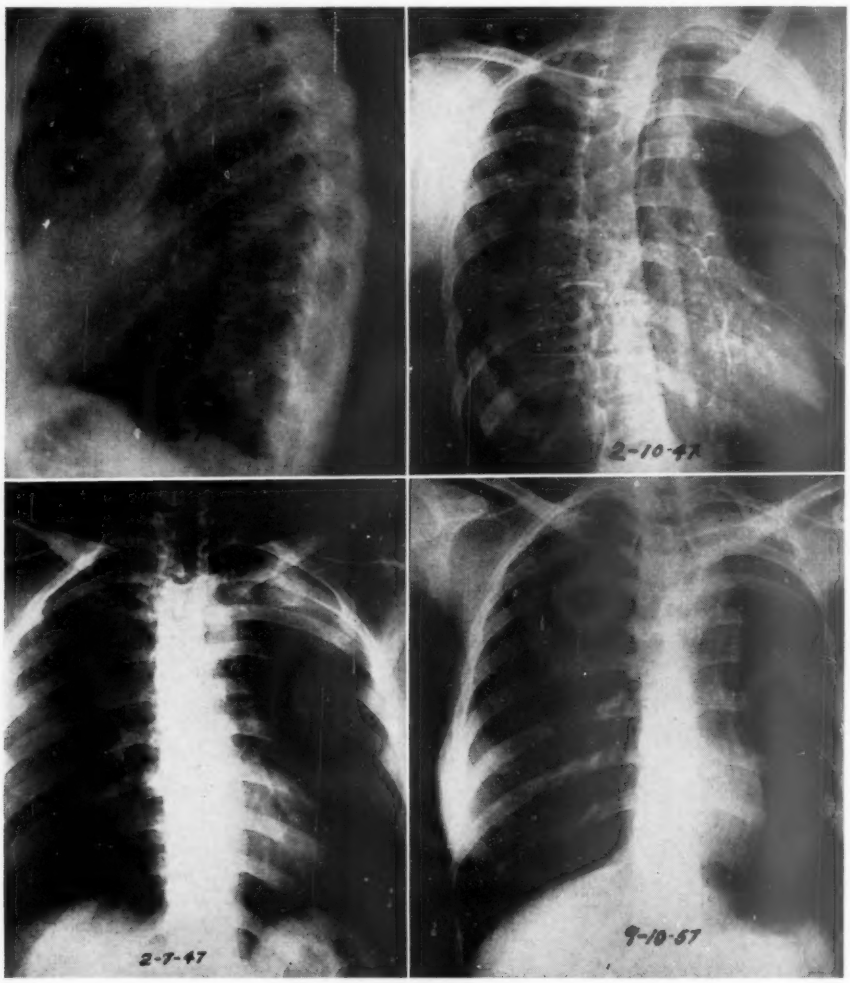
The next hospitalization was at Research and Educational Hospitals of the University of Illinois on Feb. 13, 1941. He had complained of clubbing of his fingers for 6 months, aching in shoulders, and swelling of his right ankle for 5 months. There had been some coughing over the preceding 2 months with 2 episodes of hemoptysis. A chest x-ray had been taken before admission because the roentgenologist suspected an abnormality associated with his osteoarthropathy. This revealed a density as seen in Fig. 6, *A*.

Physical examination was not significant except for the diminished breath sounds to the left of the sternum, the clubbed fingers, the amputated limb, and the ankle edema.

Laboratory data were not remarkably altered.

A left upper lobectomy utilizing tourniquet technique was accomplished on Feb. 18, 1941 (Fig. 6, *B* and *C*). The histologic appearance of this specimen was identical to that of the left femur (Fig. 5, *C*). The patient was discharged from the hospital in approximately 5 weeks with an essentially uneventful postoperative course and has remained well to date, over 17 years since his lobectomy.

A.



B.

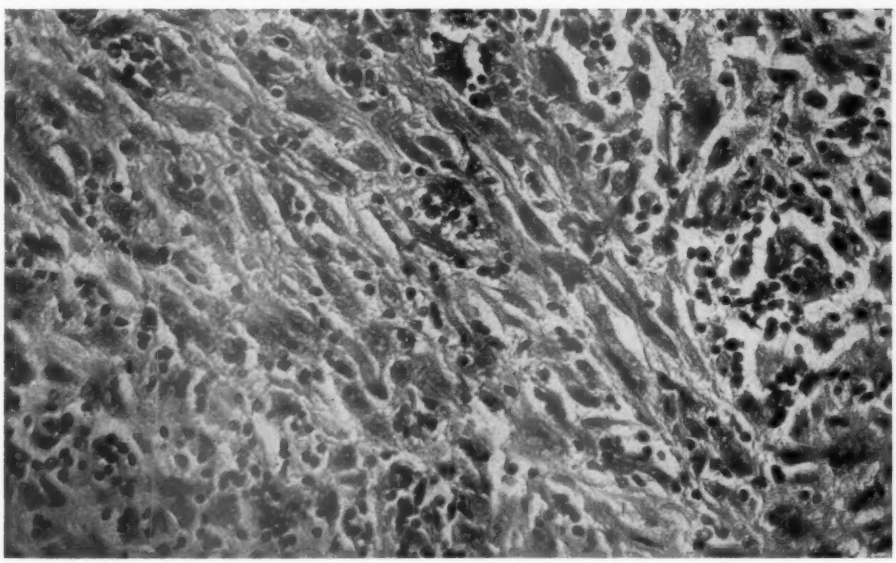
Fig. 7.—*A*, Lateral and oblique projections reveal the tumor in the left upper lung field. *B*, Pre- and postoperative films. Note absence of portions of ribs 2 and 3 in film of 9-10-57.

Case 4 is briefly abstracted since this patient also represents a rather remarkable survival.

Case 4 (miscellaneous sarcoma series): This patient (H. H.) was a 36-year-old white housewife who was admitted to Research and Educational Hospitals of the University of Illinois in February, 1947. She gave a history of having had a mobile x-ray taken in June, 1946, at which time a "spot" was discovered. In December, 1946, she noted the onset of

cough and once in December and once in January an episode of hemoptysis occurred. In recent weeks a slight pressure sensation developed over the lateral and anterior aspect of the left chest.

A.



B.

Fig. 8.—*A*, Cut surface of tumor in upper lobe. *B*, Note spindle cell character of tumor.

During the years 1939 through 1941, she had had 4 or 5 operations for a recurrent tumor mass at the lateral aspect of the arm and forearm at and just above the right elbow. Tissue reports of these lesions were spindle-cell sarcoma.

Physical examination revealed multiple, slightly pigmented, verrucous lesions over the trunk, anterior and posterior with a number of "café au lait" spots as well. There

TABLE VI. MISCELLANEOUS CARCINOMA

PATIENT	AGE	SEX	SITE	TYPE	TREATMENT	DATE	INTERVAL	DATE	PULMONARY SURGERY	STATUS
1. G. M.	43	M	Left hand	Squamous	Multiple excisions, axillary dissection	3-49 9-49 10-49	1 yr. 1 mo.	10-51	Left lower lobe	Dead— 1 yr. 2 mo.
2. J. D.	65	M	Lower lip	Squamous	Excision; right neck dissection	10-50	1 yr. 7 mo.	5-52	Inoperable	Dead— 4 mo.
3. A. M.	58	M	Tongue	Squamous	Irradiation and partial glossectomy	7-49 9-49 2-50	2 yr. 9 mo.	11-52	Right lung	Dead— 2 yr. 1 mo.
4. H. J.	55	M	Right maxillary sinus	Squamous	Resection	9-54	1 yr.	9-55	Left lower lobe	Living— 2 yr. 7 mo.

was a 14 cm. healed surgical scar over the lateral aspect of the forearm extending to midway up the arm. There was slight dullness with diminished breath sounds at the apex of the left chest.

The laboratory findings were essentially normal. Sputum studies were negative for tuberculosis. Chest x-rays (Fig. 7, *A* and *B*) demonstrated changes in the left apex and these were more pronounced when compared to her earlier film in December.

A bronchoscopic examination revealed no abnormalities and on Feb. 18, 1947, removal of the upper lobe of the left lung with attached portions of the second and third ribs was accomplished. The specimen and the histologic character of the lesion are shown in Fig. 8, *A* and *B*.

Miscellaneous Carcinoma.—Our last series has been listed as miscellaneous carcinoma for purposes of convenience. The tumors have varying sites of origin, and of exceptional interest was Case 1, which was an example of an arsenical dermatitis with secondary malignant degeneration not only on the left hand but also on the left foot.

Only one patient was salvaged in this group and this man had undergone a series of deforming procedures upon his maxillary sinus, which was the primary site.

DISCUSSION AND SUMMARY

In this group as a whole, no distinct pattern was apparent as to symptomatology. A fair number of patients were unaware of recurrence until either mobile survey or routine follow-up roentgen films were taken. Two patients were troubled with joint symptoms characteristic of pulmonary osteoarthropathy and this disappeared after resection of the lesion.[14] Others became quite distressed with symptoms ranging from cough and hemoptysis to severe dyspnea. It was usually in the latter group that bronchoscopy was of importance.

Almost all the patients had this procedure done prior to surgery and in approximately 30 per cent a positive diagnosis was established on tissue study. Two of these, however, were by Papanicolaou stain. The positive results were all limited to the carcinoma cases, although compression of narrowing was usually the finding in the sarcoma group.

This would emphasize the importance of this procedure and one example not included in the group is that of a patient with metastatic colon tumor in whom positive tissue was obtained from each main bronchus, although the tumor was visible only on one side in the x-ray film.

Furthermore, one must not think of metastatic disease just as single or multiple peripheral parenchymal nodules. The lesion may be central, and bronchial, and may closely resemble primary lung cancer.

Likewise the roentgen appearance may simulate primary disease; although in the patient with advanced illness, the bilateral circumscribed densities of varying sizes are quite characteristic.

Although 4 patients in this series had 2 procedures, no patient was considered for surgery if there were several widely scattered densities throughout both lung fields. A thoracotomy was performed in one patient not included in this group in whose chest film 3 circumscribed densities were discovered. This patient had had a previous hysterectomy for adenocarcinoma of the body of the uterus and our clinical impression was that she had metastatic disease. However,

these lesions were all granulomatous and resected by segment or subsegmental technique. This re-emphasizes Strieder's comment about such benign entity possibilities.

Notwithstanding the very small percentage of "good fortune" cases as the above would represent, the roentgen examination remains as the most important tool in the diagnosis of the pulmonary metastasis and, where the x-ray is abnormal, delay of thoracotomy may be disastrous. Case 1 of the colon series is an example of this. Strohl and Pontius[13] previously reported this patient in their paper "Polyposis of the Colon."

It was not possible to obtain tissue material on all patients in the group, although all but one patient had had previous treatment for the primary lesion, surgical and/or pathology reports having been obtained in most of these. The interpretation of the metastatic material was most readily made in the sarcoma group since this type of lesion in the lung is very uncommon as a primary process. We do have 5 such problems which are to be reported at a later date. None of these 5 were included in this series, however.

The metastatic epithelial tumors were most readily identified when the colon was the source and 4 of this group had the diagnosis established on bronchoscopic material.

Of the lung lesions seen associated with uterine malignancy, 2 patients had squamous and one glandular disease. Although it could be possible for the lung lesions to represent a second primary, it would seem most logical to consider these as metastatic.

Probably the most difficult group from this standpoint were the patients with breast cancer since the lung material demonstrated distinct tendency to resemble squamous lesions.

We have not included patients who had previous laryngectomy for epidermoid cancer prior to pulmonary resection for similar disease. It is our feeling that these represent multiple foci of origin in varying sites of the respiratory tract.

Accordingly, of these 50 patients who were operated upon, 48 were resected, an operability rate of 96 per cent. This high figure is due to a radical approach to the problem, our feeling being that the essence of the surgery was the removal of large tumor masses even if portions of the chest wall, diaphragm, pericardial sac, or atrial wall need be removed to gain this end. In 2 cases with recurrent laryngeal involvement and paralyzed left vocal cords, resection was accomplished with 13- and 15-month survivals. There were 5 deaths for a mortality of 10 per cent over-all: 3 following pneumonectomy, one lobectomy, and one the completion of pneumonectomy with removal of the remaining lobe for recurrence following left upper lobectomy.

A breakdown of the survivors is represented in Table VII and the duration in Table VIII.

The survivor group represents about 32 per cent of the entire series. However, on the basis of 3-year survival, this figure is reduced to approximately 14 per cent.

The comparison of the 2 general groups is found in Table IX.

TABLE VII. SURVIVORS

GROUP	TOTAL	LIVING	DEAD
Kidney	6	0	6
Breast	11	4	7
Colon	8	4	4
Female genitalia	7	4	3
Miscellaneous sarcoma	14	3	13
Miscellaneous carcinoma	4	1	3
Totals	50	16	34

TABLE VIII. DURATION

MONTHS	TOTAL
5-12	4
13-24	4
25-36	2
37-48	1
49-60	1
61-72	1
73-84	1
134	1
206	1
Total	16

TABLE IX

	TOTAL	POST-OPERATIVE DEAD	INOPERABLE	NET	LIVING AND WELL	PER CENT
Epithelial	33	4	1	28	12	42.7
Mesothelial	17	1	1	15	4	26.6

From these small numbers it would appear that carcinomatous lesions would offer the more favorable outlook.

Another feature which is suggested by the high operability rate is the tendency for the metastatic lesion to remain localized within the lung (with the exception of breast carcinoma as pointed out by Minor).[10] Utilizing the same radical approach on primary lung carcinoma does not give this degree of resectability. It is likely that the metastatic lesions have a greater tendency to remain asymptomatic and hence grow to a large size before symptoms occur. This would again emphasize the need for repeated x-ray studies of the chest as routine follow-up in all patients with resective surgery for malignancy. In the inoperable patient in the sarcoma group, no follow-up films were ever taken until symptoms occurred.

The palliation provided has been stressed much by previous writers as to require but little comment. Generally in the sarcoma group, symptomatic relief was dramatic but in many cases of short duration until the recurrence developed. However, in 3 colon cases the patients were relieved of respiratory symptoms until very rapid terminal courses developed associated with brain metastases.

The interval of time between the first and second treatment measures would appear to be a factor in the survival of the 3 abstracted cases since at least 5 years elapsed in these patients. However, poor results were seen in a number of patients with breast disease which had been treated at least 5 years prior to

lung surgery, and one patient with an ovarian tumor had a lung resection within 2 years of the first surgery and represents over 6 years' survival. Prognostically the time interval is not an absolute factor.

CONCLUSIONS

Certain generalities are suggested by an appraisal of our patient material.

1. The resectability rate in metastatic pulmonary disease is exceedingly high.

2. There is perhaps a slightly better prognosis for carcinomatous lesions than sarcoma as a group.

3. Of the carcinoma metastases, the colon appears to offer the more favorable diagnosis.

4. A lesion of the lung in an individual with previous breast carcinoma is more likely to represent metastasis rather than a second primary tumor.

5. Although the sarcoma group has a generally poor outlook, the behavior of any one type is entirely unpredictable.

6. A survival rate of 32 per cent of the group would appear to justify the procedure as an acceptable modality.

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Editorial

Conducted by I. S. Ravdin, M.D.

What Is "Optimum Flow Rate"?

With the rapidly expanding use of pump-oxygenators, a recurrent problem has been the choice of extracorporeal flow rate during the period of perfusion. A great deal of discussion has centered about "what is the optimum flow rate and what, in actual figures, are 'high' and 'low' flow rates?" There is now sufficient evidence at hand to begin formulation of some practical guides to choice of flow rate.

In 1952, Andreason and Watson[3] reported the survival of animals maintained for brief periods of time on only the circulation available from the venous return through the azygos vein, thereby providing a basis for the initiation of open heart surgery during temporary extracorporeal circulation. Lillehei and his associates[12] brilliantly extended this study of the "azygos principle" into practical utilization, perfusing patients with a portion of the circulation of a donor. Subsequently, the "low flow principle" has been widely adopted in the use of artificial pump-oxygenators. Use of a low flow rate enjoys the advantages of (1) requiring machines of less pumping and oxygenating potential, (2) producing less blood loss during the period of open heart surgery, and (3) requiring less priming blood. On the other hand, a high flow rate empirically has seemed to be more physiologic and an occasional voice has been raised, such as that of Kirklin,[7] advocating the use of flow rates comparable to that of the patient's normal basal cardiac output.

In terms of physiologic response, it is not unreasonable to compare extracorporeal circulation with a low flow rate to hemorrhagic shock. In each case the circulating blood volume is reduced and the circulatory rate is subnormal. As in shock, laboratory and clinical studies have shown that low flow rates result in total body hypoxia,[2] a metabolic acidosis,[5, 6] impairment of renal[11] and hepatic function,[1] and abnormalities in cerebral electrical activity.[9] These same abnormalities have been found to be reduced or abolished by perfusion at high flow rates.[2, 4, 10, 11]

What, then, constitute "high" and "low" flow rates in a given patient?

Studies in dogs have shown that oxygen consumption is maintained at control levels with flow rates above 100 ml. per kilogram per minute, and that there is a progressive fall in oxygen utilization below this figure.[2] At flow rates above 100 to 110 ml. per kilogram per minute, renal plasma flow and glomerular filtration rate continue at normal levels; at 50 ml. per kilogram per

minute, there is almost complete suppression of these functions.[11] The rise in lactic acid and fall in blood potassium levels, observed routinely at flow rates from 25 to 70 ml. per kilogram per minute, are reduced or abolished with flow rates above 100 ml. per kilogram per minute.[10]

These figures can be examined in the light of the resting cardiac output in the anesthetized dog which ranges from 130 to 160 ml. per kilogram per minute. On this basis, a flow rate of approximately 75 per cent of the basal cardiac output or higher appears to provide essentially normal organ function and could be regarded as a "high flow rate." Those below this point produce increasing disruption of physiologic processes and could be considered as "low flow rates." These figures agree rather well with studies of oxygen consumption during reduced cardiac output and hemorrhagic shock and the observed physiologic derangements occurring during these states.[2, 13] It seems doubtful that, at comparable circulatory rates, one could expect artificial circulation with a pump-oxygenator to produce a better physiologic state than is provided by autogenous cardiac circulation.

Although direct transposition of experimental data to patients may not be entirely valid, clinical studies during open heart operations have shown similar results.[8] At levels of circulatory rates (in terms of basal cardiac output) comparable to those mentioned in dogs, the same abnormalities develop and an inverse relationship has been demonstrated between flow rate and metabolic acidosis and hypoxia.

Although it is known that patients may tolerate a certain duration of shock and yet survive, no one would argue that it is a desirable state or one to be deliberately encouraged. It is no more reasonable to suppose that extracorporeal circulation with a subnormal flow rate is desirable except from the standpoint of increasing the ease of technical performance and permitting the use of less-than-adequate pump-oxygenators. When low flow rates are used it should be with the realization that the factor of time is of great importance, that the tolerance is limited, and that physiologic abnormalities are being created which subsequently must be corrected. The only possible justification for their use must lie in the possibility of a protective redistribution of blood flow at low perfusion rates which could maintain adequate blood flow to the vital organs at the expense of the less vital. Further studies of this subject and of the actual tolerance to various levels of circulatory rate are in progress; until these factors are better understood, we must conclude that the safest course to follow is the maintenance of a "high flow."

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

HISTORICAL LANDMARKS IN THE TREATMENT OF BURNS

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THERMAL burns are nearly the commonest single lethal injury today, accounting for at least 6,000 deaths per year, not including deaths from conflagaration.[19] Their incidence in different places and times historically reflects various factors, such as climate, housing conditions, industry, and manners of warfare. Burns represent a good subject for a historical study, because comparisons can be made down through the ages; for instance, in an ancient case history, a burn of a given extent can often be recognized and assigned a percentage value.

The requisites for success in the care of the burn patient may be summarized as follows: (1) adequate treatment of the primary and secondary shock, (2) adequate treatment of the so-called toxemia phase, and (3) adequate treatment of the chronic phase, which means achievement of skin coverage at the earliest possible time, usually by skin grafting. With maximal efforts and adherence to these principles, a certain percentile salvage of extensively burned patients can be expected, a value which is fairly constant from clinic to clinic. The history of the development of these principles is the subject of the present essay.

Many aspects of the early history of the treatment of burns are well described in an excellent article by Cockshott[7] of Edinburgh, and much of what follows is derived from his study. He relates the views of Paulus of Aegina, a Byzantine of the seventh century, A.D., whose writings reflected Greco-Roman thought and who utilized various emollient preparations with bizarre ingredients. As an example of the unusual concoctions employed by the ancients, a quotation from Pack's book[27] follows:

> The salve of Paracelsus for wounds and burns is even more impossible. It consisted of the fat of very old wild hogs and bears, heated half an hour in red wine, then dropped into cold water, which was next skimmed and the fat rubbed up with roasted angle worms and moss from the skull of a person hung, scraped off during the increase of the moon, to which were added blood stone, the dried brain of a wild hog, red sandle wood and a portion of a genuine mummy.

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Rhazes and Avicenna, representing ninth and tenth century Arabic thought, recommended the use of refrigerants locally, which certainly had the virtue of alleviation of pain. Guy deChauliac's fourteenth century opus, *Chirurgia Magna,*[14] does not cover burns, but this was a work which came fairly soon after the beginnings of the use of gunpowder.[15]

Hieronymus Brunschwig,[2] at the end of the fifteenth century, did cover the subject of gunshot wounds, but not burns. He was not an army surgeon. Giovanni de Vigo,[16] surgeon to Pope Julius II, writing in 1514 began the controversy regarding the existence of a toxin in gunpowder burns.

From some of the early case histories, it appears that burn wounds occurred more often from the mishandling of gunpowder than from actions of the enemy. Such causation is apparent in the writings of William Clowes,[6] whose book, published in 1596, was the first devoted chiefly to the subject of burns. Its title was *A Profitable and Necessarie Booke of Observations, for All Those That Are Burned With the Flame of Gun Powder,* etc. This work was in the form of a series of case histories, describing his methods of treatment, which consisted chiefly of the use of complex ointments derived from continental sources, chiefly Paré, and these in turn deriving from Greco-Roman, Arabic, and even Egyptian sources. Clowes lived from 1540 to 1604 and in London was the foremost surgeon of his time, following a colorful military career. The records of the Barber Surgeons' Company contain an account of a pardoning of Clowes for fighting in the field with one George Baker. His book was written not in Latin, but in the vernacular, and contains a defense of his choice. A part of his first case report is quoted.

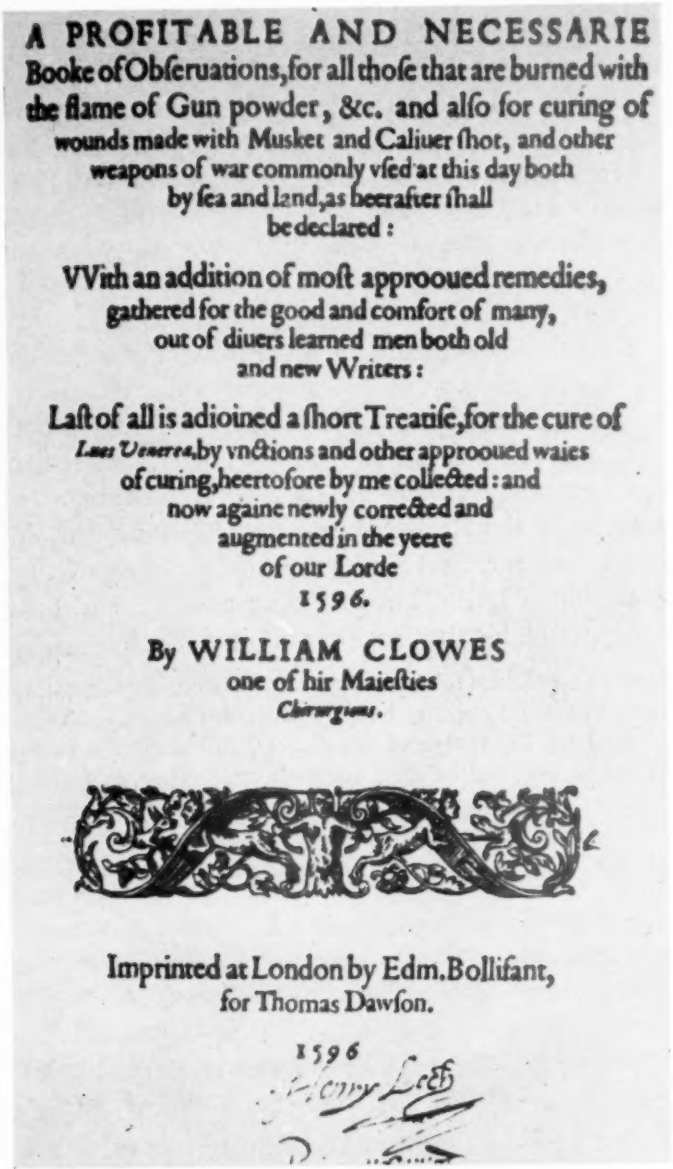
> It happened in Anno 1577, two gentlemen were drying gun powder in a brass pan, who (as it did appear) had no consideration unto the over heating of the pan, but without knowledge of the danger, and care of themselves did continually stir the powder with their hands. It chanced so, that the powder upon a sudden fired, inherewith they were most greviously burned, both hands and face, with their bodies and clothes, which caused them to make a most lamentable crying: and being heard by divers in the same house, who perceiving their chamber to be in a great smoke and smell of gun powder, presently entered in, and with all haste that possibly might be, carried the persons burned into another room, where they forthwith did cut, rend, and tear off all their clothes from their bodies: otherwise without their helpes, no question but they had been burned to death.

He did not recognize the various degrees of burn, but did employ some five different complex preparations on the different parts of the burned individuals.

In 1597 there appeared a book on surgery from Scotland, the first major work on the subject by one from this country.[23] Peter Lowe was the author, who lived from about 1550 to 1613. He was well known for his efforts to eliminate from Scottish medical practice quackery, of which he recognized eight basic types. In connection with improving the standards he founded the Faculty of Medicine and Surgery of Glasgow. His major contribution in the

treatment of burns would seem to be his attempt to "heale all kindes of burning in a short time with one emplaister onely," which represents a recommendation toward avoidance of too frequent changes of dressing.

In the early seventeenth century there was published a book in Basel by Fabricius Hildanus (Wilhelm Fabry) entitled *DeCombustionibus*,[20] in which



A PROFITABLE AND NECESSARIE
Booke of Obſeruations, for all thoſe that are burned with the flame of Gun powder, &c. and alſo for curing of wounds made with Musket and Caliuer ſhot, and other weapons of war commonly vſed at this day both by ſea and land, as heerafter ſhall be declared:

VVith an addition of moſt approoued remedies, gathered for the good and comfort of many, out of diuers learned men both old and new Writers:

Laſt of all is adioined a ſhort Treatiſe, for the cure of *Lues Venerea*, by vnctions and other approoued waies of curing, heertofore by me collected: and now againe newly corrected and augmented in the yeere of our Lorde 1596.

By WILLIAM CLOWES
one of hir Maieſties *Chirurgions*.

Imprinted at London by Edm. Bollifant, for Thomas Dawſon.

1596

Fig. 1.—Frontispiece of book by William Clowes.

he recognized the three degrees of burning ("levissiman, mediocrem, and insignam"). He also dealt with the problem of management of late burn contracture.

Next upon the scene was Richard Wiseman,[39] who lived from 1622 until 1676. This prominent British surgeon, who served for a while with the Dutch

navy, is credited with achieving the separation of the surgeons from the Barber-Surgeons Company. His place in surgery has been compared to that of Sydenham in medicine, and he has been called the "Paré of England," to whose writings on the subject of burns he added little. A description of a case from his book follows:

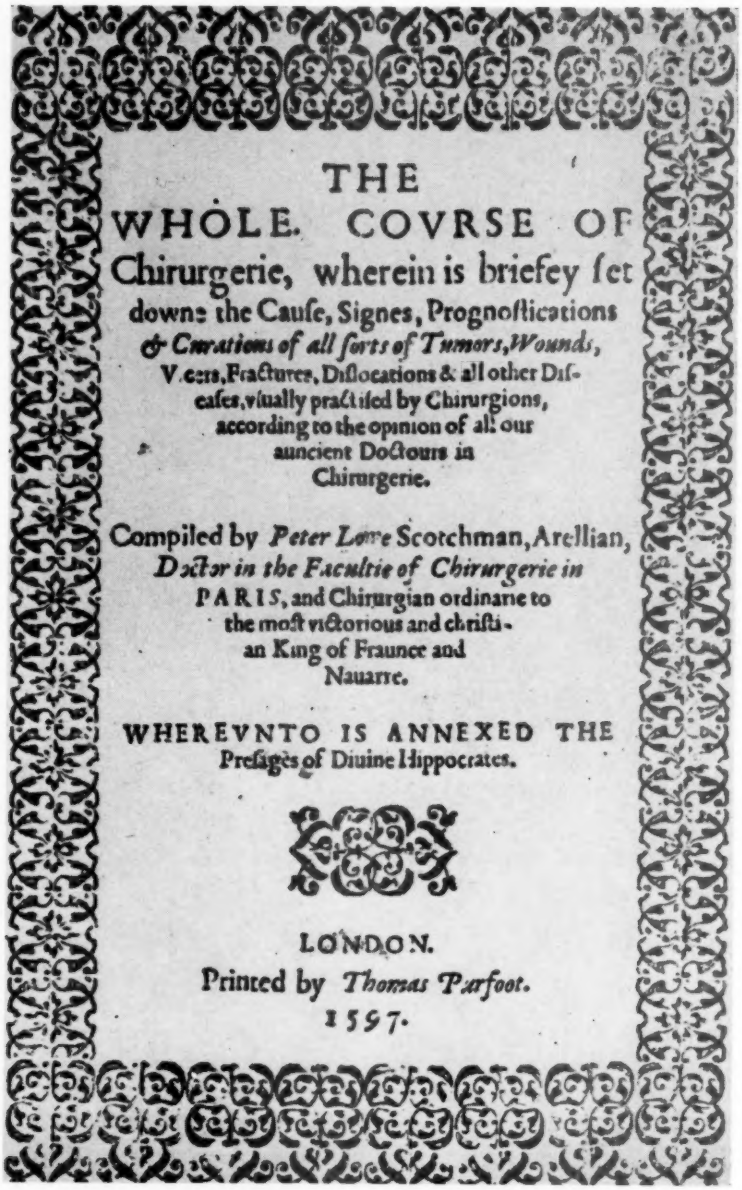
Fig. 2.—Portrait of Peter Lowe.

> A Souldier in the time of service being in the Fort-Royall at Worcester, hastily fetched his bonnet full of gun powder, and whilst he was filling his Bandeliers, another Souldier carefully bestrides it to make a shot at one of the enemies which he saw lying perdue. In firing his musket, a spark flew out of the pan, and gave fire to the powder underneath him, and grievously burned the hands, arms, breast, neck and face of him that was filling his Bandeliers. And so to himself he likewise was burned and scorched in all the upper parts of his thighs, scrotum, the muscles of the abdomen, and coats of the testicles to the erythroides, so that the cremasters were visible. And indeed it was to be feared, that when the eschar should cast off from his belly, his bowels would have tumbled out. We dressed the severall parts of them both with mel saponis and embrocated the parts about *cum ol. ros. and albumine ovor.* beat together, and let them bloud.

He goes on to state that, although he did not stay to witness this, the latter patient was cured and the former escaped out of town.

Occasionally a contribution to medical lore comes from an unexpected source. One David Cleghorn,[5] and Edinburgh brewer, became a recognized

expert in the treatment of burns early in the eighteenth century. He is to be credited with a recognition of the fact that purgation, widely practiced at the time, was harmful to the burned patient.



THE
WHOLE COVRSE OF
Chirurgerie, wherein is briefey ſet
downe the Cauſe, Signes, Prognoſtications
& Curations of all ſorts of Tumors, Wounds,
Vlcers, Fractures, Diſlocations & all other Diſ-
eaſes, vſually practiſed by Chirurgions,
according to the opinion of all our
auncient Doctours in
Chirurgerie.

Compiled by *Peter Lowe* Scotchman, Arellian,
Doctor in the Facultie of Chirurgerie in
PARIS, and Chirurgian ordinarie to
the moſt victorious and chriſti-
an King of Fraunce and
Nauarre.

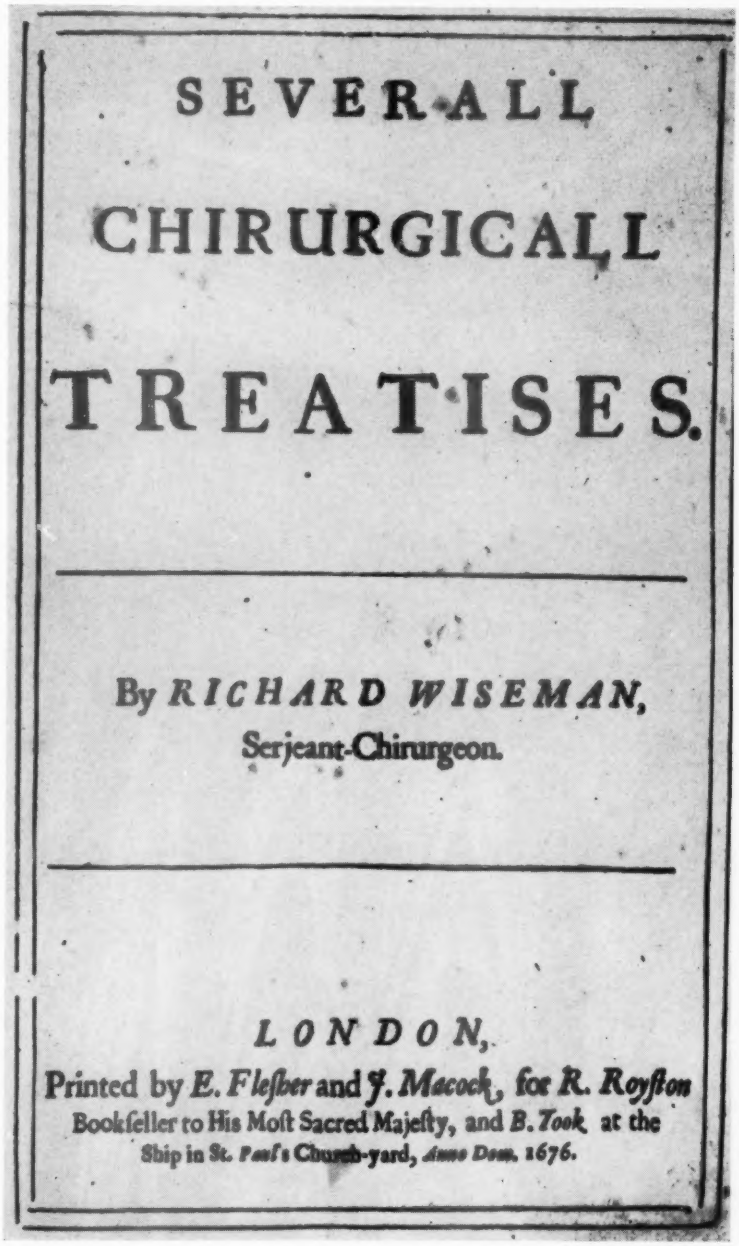
WHEREVNTO IS ANNEXED THE
Preſages of Diuine Hippocrates.

LONDON.
Printed by *Thomas Purfoot.*
1597.

Fig. 3.—Frontispiece of book by Peter Lowe.

Sir George Ballingall published his book[1] on military surgery, the substance of which was a course at the Edinburgh school in 1833. His description of the natural history of the burn wound was lucid, as was his account of the fate of the burned patient. Concerning the early death he wrote, "he sinks from causes which we cannot explain," a statement which is still true. The

deaths at 10 or 12 days he recognized as usually being of a febrile nature, now recognized as being frequently on the basis of a bacteremia. The later deaths, those occurring 3 to 6 weeks after burn, he described as "sinking in a hectic


SEVERALL
CHIRURGICALL
TREATISES.

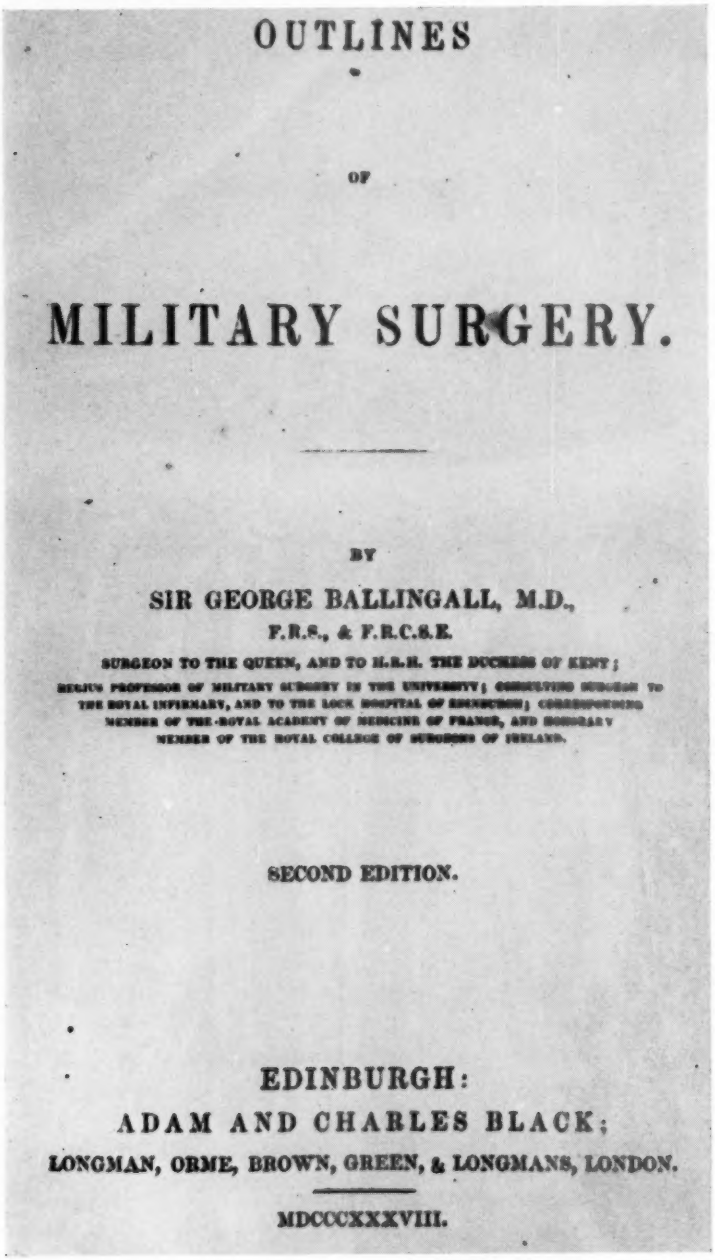
By RICHARD WISEMAN,
Serjeant-Chirurgeon.

LONDON,
Printed by E. Fleſher and J. Macock, for R. Royſton
Bookſeller to His Moſt Sacred Majeſty, and B. Took at the
Ship in St. Paul's Church-yard, Anno Dom. 1676.

Fig. 4.—Frontispiece of book by Richard Wiseman.

state, exhausted by a profuse discharge of matter from an extensive suppurating surface." Despite this clear account, however, he continued the customary recommendation for purgation and blood letting as important aspects of treatment.

In 1797 there appeared a book entitled *An Essay on Burns* by Edward Kentish[21] of Newcastle-on-Tyne. This physician was largely concerned with the care of Scottish coal miners in the area, and the dedication of his book is to the owners of the collieries. A portion of this is quoted:



OUTLINES

OF

MILITARY SURGERY.

BY

SIR GEORGE BALLINGALL, M.D.,

F.R.S., & F.R.C.S.E.

SURGEON TO THE QUEEN, AND TO H.R.H. THE DUCHESS OF KENT;

REGIUS PROFESSOR OF MILITARY SURGERY IN THE UNIVERSITY; CONSULTING SURGEON TO THE ROYAL INFIRMARY, AND TO THE LOCK HOSPITAL OF EDINBURGH; CORRESPONDING MEMBER OF THE ROYAL ACADEMY OF MEDICINE OF FRANCE, AND HONORARY MEMBER OF THE ROYAL COLLEGE OF SURGEONS OF IRELAND.

SECOND EDITION.

EDINBURGH:

ADAM AND CHARLES BLACK;

LONGMAN, ORME, BROWN, GREEN, & LONGMANS, LONDON.

MDCCCXXXVIII.

Fig. 5.—Frontispiece of book by Sir George Ballingall.

I am afraid the following remark will be found as true as it is extraordinary, that during a period exceeding 600 years that the coal trade has flourished in this neighborhood not a single remark upon the subject* has preserved upon record,

*That is, the treatment of burns.

> though during that period some of the first surgical and medical men in the kingdom have had the phenomena constantly before their eyes. What causes can be assigned to such inattention to the interests of humanity? Ignorance and prejudice on the part of people, and disgust on that of the faculty; these appear to be the principal causes why so little attention has been paid on the part of the practitioners.

Much of the theoretical aspect of this book is derived from the teachings of Boerhaave, a Hollander who taught medicine around the beginning of the eighteenth century.

In Cockshott's review[7] he mentions a dissertation by Robert Hornby in 1833, in which the latter took cognizance of the harmful effects of purgation and bleeding. He apparently recognized that the shock of burns was not unlike that of peritonitis, and this was the basis of his precocious advice against measures which would produce further dehydration.

Casualties in large numbers are a stimulant to interest in specific medical problems, as was the case in 1857 when an explosion occurred at the Pyrotechnical Laboratory in Frankfurt-am-Main. Passavant[30] was the physician in charge, and he treated with saline baths the 13 patients who survived; 7 died in the fire.

Somewhat later, Tappeiner[35] of Munich, in 1881, recognized from autopsy studies certain fundamental features of the pathophysiology of extensive burns, namely, the concentration of the blood which occurs. This was manifested by its reduced water content, increased hemoglobin, and decreased bleeding volume. Such observations were very fundamental to successful treatment of burns in pointing out the need for replacement of some of the lost elements. By 1901 fair cognizance of these needs must have been taking place in some circles, because Parascandolo[29] of Naples in 1901 utilized NaCl in the treatment of 3 burn patients. One may speculate as to whether he had contact with Guido Bacelli,[4] a contemporary, who was the leading figure in Italian medicine at the time. Bacelli was an important promoter of the use of intravenous fluids.

Parascandolo also did some fanciful work on the development of an antitoxin against alleged ptomaines from burned skin, which was said to protect experimental animals. This toxic theory of burn deaths was widely upheld, so much so that Robertson and Boyd[33] of Toronto utilized exsanguination transfusion in the treatment of patients. Weidenfeld[38] of Vienna in 1902 also utilized NaCl solutions parenterally in the treatment of burns.

By 1905 an American, Hardor Sneve[34] of St. Paul had recognized the importance of saline administration parenterally and his article in the *Journal of the American Medical Association* of that year advocated also the concept of *early* coverage by skin grafting. The evolution of this concept was one of two main channels of thought leading to present-day burn management.

A brief review is in order of the background of skin grafting, the first widely used form of successful autotransplantation of tissue in the human. Upon successful early skin grafting depends the life of the extensively burned patient, after he has been carried through the earlier hazards by proper

therapy. The ancient Hindus are known to have carried out skin grafting. Padgett[28] tells the story of a nineteenth century charlatan named Gamba Curta who cut off a piece of skin, passed it around among onlookers, and then re-applied it. This was done to demonstrate the healing powers of an ointment she was promoting. Dr. Bunger[3] in 1823 carried grafts from thigh to nose, and Dr. J. Warren Mason[24] of Boston in 1843 did the same. It is of interest to note that both hair roots and blister epithelium had been tried as methods of skin grafting. Apparently skin grafting came upon a firm basis with the publication by J. L. Reverdin,[31] in 1872, describing his success with tiny epidermic grafts. Reverdin was a Swiss, who at the time was a house physician on Guyon's service at the Hôpital Necker in Paris. His paper was presented to the Société Imperiale de Chirurgie in 1869.

TABLE X. (A)—*Mortality of Thermal Injury Involving More than 25 Per Cent of Body Surface.* (Ages Less Than 61 Years)

Series	Source	Therapy	Number of Individuals	No. Dead	Mortality %
I	Weidenfeld Vienna, 1902	Exposure or water bed (No supportive therapy)	41	41	100
II	Weidenfeld and Zumbusch Vienna, 1905	Exposure or occlusive dressings—or water bed. Small amounts of 0.9 NaCl subcutaneously 250 ml. to 3 L.	12	11	91
III	Sneve St. Paul, Minn., 1905	Exposure plus zinc acetate powder. Large volumes of 0.9 NaCl by vein, by infusion (subcutaneously) by mouth, by rectum	24	13	54
IV	Riehl Vienna, 1926	Carron oil—occlusive dressings or water bed, 0.6% saline by subcutaneous infusion and enema, small transfusions of blood—many were exchange transfusions	18	14	77
V	Rosenquist Stockholm, 1942–1946	Variable local treatment: triple dye; occlusive dressings; plasma and/or dextran	29	16	55
VI	Dallas, Tex., plus St. Louis, Mo., 1944–1946	Debridement under anesthesia sulfathiazole ointment or vaseline under pressure dressings. Plasma according to hematocrit or surface area rule	83	39	47
VII	Bull Birmingham, Eng. 1944–1948	Occlusive dressings, Sterile room, Plasma	51	25	49
VIII	Dallas, Tex., plus Kankakee, Ill., (Robinson) 1946–1951	Dry fine meshed cotton gauze without debridement under an occlusive dressing—Hartmann's solution by vein. Buffered saline by mouth and whole blood, i. v.	105	34	32

Fig. 6.—A table from article by Carl A. Moyer, reproduced with permission of author and publisher. (Moyer, Carl A.: An Assessment of the Therapy of Burns, Ann. Surg. 137: 628-638, 1953.)

In 1872 L. Ollier[26] reported success with larger pieces, even up to 4 by 8 cm. Karl Thiersch[36] in 1874 reported the use of deeper slices of skin, deliberately taking some dermis along with the epidermis. Soon thereafter, around 1875, Wolfe[40] of Edinburgh and Krause[22] of Germany were able to report successful transfer of even full-thickness grafts of skin.

Apparently, however, much of the early grafting prior to World War I was done with small pieces of skin, larger grafts being much more difficult to obtain. The skill necessary to slice free hand a large sheet of skin of proper depth was not possessed by many surgeons. The work of Vilray Blair, James

Barrett Brown, and John Staige Davis contributed greatly to the promulgation of skin grafting, and in 1939 Padgett developed the dermatome. The wide utilization of extensive skin grafting for burns in the twentieth century has doubtless saved many lives.

The second important channel of thought to be followed is that of fluid replacement therapy. It was mentioned that Hardor Sneve in 1905 had advocated not only early skin grafting, but also the administration of saline, both subcutaneously and by infusion. Moyer's comparative historical study[25] of burn mortality over the years indicates what good survival (54 per cent) Sneve[34] was able to achieve in burns of over 25 per cent.

Fig. 7.—Portrait of Underhill, reproduced with permission of author and publisher from book by Harkins.[19]

Complete appreciation of the magnitude of fluid losses in burns awaited the studies of Frank Pell Underhill[37] (1877-1932). This man, a professor of pharmacology and toxicology, had done excellent work in several fields, among them a study of war gases. In 1921, there occurred a catastrophic fire at the Rialto Theatre in New Haven. Twenty people were seriously burned, of whom four died. Working with the late Dr. S. C. Harvey, Underhill[37] studied

these patients, carrying out determinations of hemoglobin, hematocrit, and chlorides. The findings were summarized in a 1930 article, "The Significance of Anhydremia in Extensive Surface Burns," which summary covered the clinical results as well as the findings from a series of animal experiments which followed. His interest in the pathophysiology had been stimulated by the theatre fire, and he investigated quantitatively the magnitude of the fluid losses. For instance, he was able to point out that an animal burned over one-sixth of its body surface could lose up to 70 per cent of its circulating blood volume in 24 hours. He was able to translate his calculations to the adult human and recognized that the patient with extensive thermal injury might require 4 to 8 L. of normal saline. Underhill also carried out studies to disprove quite conclusively the previously held theory that there was a toxin released from the burned skin. His analysis of the fluid in blisters led to recognition of the protein content and paved the way for its replacement as methods became available. In his 1930 article he made a somewhat prophetic remark about the local care of the burn wound: "In the treatment of the injured area the query may be made: why stop drainage by application of substances like trinitrophenol or tannic acid? Why not treat a burn like any other wound?"

EXTRA New Haven Sunday Register.

MANY LIVES BELIEVED LOS
IN RIALTO THEATRE FIR

PROBABLY THE WORST THEATRE FIRE CATASTROPHE THE CITY HAS E
EXPERIENCED--EVERY HOSPITAL CROWDED WITH INJURED--SCORES OF
ANXIOUS RELATIVES AND FRIENDS STORM HOSPITALS IN QUEST
OF INFORMATION ABOUT THEIR MISSING ONES.

Fig. 8.—Front page of New Haven Register of Nov. 27, 1921, describing the tragic theatre fire.

About the same time one other worker was studying the fluid and electrolyte shifts in the burned organism and expressing his ideas as to the amounts of intravenous saline solutions to be used. This was E. C. Davidson[11] of Detroit (1894-1933), who wrote around the mid-1920's. He was seeking some method of sealing the burn surface and came upon tannic acid as a protein coagulant, a method of burn treatment which held sway until its liver toxicity was demonstrated.[12]

There existed and still does persist confusion as to the value of whole blood in the early treatment of the burn patient, confusion based upon the

fact that the patient already has a high hematocrit. Among the earliest to use this substance was Riehl,[32] the senior, of Vienna. Later his son wrote on the subject. In a book on burns, published in 1931, George Pack[27] recommends the use of blood only in connection with the treatment of shock. Pack's book was a good review of the state of knowledge on the subject at the time. Those who could not accept the rationale of whole blood could accept the use of plasma, and with increasing availability this substance became widely used. The names of Daniel Darrow[10] and J. Russel Elkinton[17] are to be mentioned in connection with the development of formulas for estimating the amounts of plasma to be used.

In 1942 was published a book on burns by Henry Harkins[19] which was a scholarly treatise. Certain of the historical leads in this essay are from Harkins's book. Some contemporary figures are to be mentioned in bringing this account up to the present. Carl Moyer of St. Louis has critically analyzed the treatment of burns from an historical viewpoint.[25] The Surgical Research Unit of the U.S. Army in San Antonio[13] has centralized the care of burn patients and learned many important lessons.

The studies of Cope and Moore of the Coconut Grove fire victims contributed greatly to our understanding of the problems of fluid balance.[9] The late Everett Idris Evans of Richmond carried out clinical and laboratory studies directed toward clarification of the replacement needs of the burn victim, and simplified practical formulas have resulted.[18] The names of other important contributors are omitted only for purposes of brevity.

In summary, an attempt has been made to trace back the historical threads of evolution of thought leading to present-day management of the burn patient, from early empiricism through the beginnings of scientific evaluation of the problem. In the future there lies a great deal of room for further advancement, since the mortality of massive burns is still very high. First, it is to be hoped that we will come to have a true comprehension of the pathophysiology involved. Only when this is achieved can supportive therapy become completely rational. Conceivably measures such as the artificial kidney or exchange transfusion may become important. Second, it is possible that means will be developed whereby the burned skin can somehow, either mechanically or enzymatically,[8] be very early removed from the extensively burned patient with predictable success thereby eliminating the depletory features of the illness, and particularly eliminating the great problem of infection. Measures such as these have been used in small area burns with success. Third, such imaginative advances, if they should occur, would require greater use of the techniques of homografting, with a hopeful eye toward the possibility that the immunologic problems may be solved. By such fanciful developments as these it is possible that the future will see a reduction in the alarming mortality from this common form of trauma.

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Book Review

CONDUCTED BY J. GARROTT ALLEN, M. D.

Clinical Proctology. J. Peerman Nesselrod. Ed. 2. Phi' ıdelphia, 1957, W. B. Saunders Company. Pp. 296 with illustrations in full color and monochrome. $7.00.

The author, an authority in his field, states in the preface that in this book he "submits . . . that part of his experience he feels may be of value to the general practitioner." The initial chapters deal with the anatomy and physiology of the terminal intestinal tract in a competent, straightforward fashion. Succeeding chapters cover the etiology, pathogenesis, symptoms, and treatment of the common anorectal diseases, hemorrhoidal disease, fistula, fissure, contracture, prolapse, and so forth. Throughout the text, anal infection is persuasively presented as the chief etiologic factor and common denominator in hemorrhoidal and other nonspecific anorectal inflammatory disease. Deserving of special mention is the chapter on clinical proctoscopy, which describes the proper use of this instrument and the diseases likely to be encountered. These descriptions are enhanced by excellent color and monochrome photographs made through the proctoscope. The various common anorectal surgical operations, preferred by the author, are illustrated and described in detail in their respective chapters. Other sections deal with pre- and postoperative care and less common diseases of the anorectum and adjacent perineal structures. A selected bibliography, at the end of each chapter, and adequate index are included.

It is difficult to find any serious criticism of this volume; its organization and balance are excellent, the style is readable yet explicit, and the material presented is up to date. The surgical procedures, preferred by the author and described in the text, have stood the tests of time and usage. This book is recommended, not only for the general practitioner, but for any physician or student who wishes to gain a sound basic knowledge of proctology.

—Thomas S. Nelsen

Calendar of Surgical Meetings

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 5-8, 1958, Royal York Hotel, Toronto, Ontario, Canada. Secretary, Dr. Robert McLaurin, University of Cincinnati, Cincinnati, Ohio.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 2-4, 1958, The Drake Hotel, Chicago, Ill. Acting Secretary, Dr. James K. Stack, 700 N. Michigan Ave., Chicago 11, Ill.

AMERICAN CANCER SOCIETY. *Annual Meeting,* Oct. 20-21, 1958, Biltmore Hotel, New York City, N. Y. Secretary, Dr. Scott Hill. Subject, cancer of the colon and rectum.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 6-10, 1958, The Conrad Hilton, Chicago, Ill. Secretary, Dr. Michael L. Mason, 40 E. Erie St., Chicago, Ill.

THE AMERICAN GOITER ASSOCIATION. *Annual Meeting,* June 17-19, 1958, St. Francis Hotel, San Francisco, Calif. Hotel Reservations must be secured by writing to Goiter Housing Bureau, Room 300, 61 Grove St., San Francisco. Secretary, John C. McClintock, 149½ Washington Ave., Albany 10, N. Y.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* Dec. 2-5, 1958, Leamington Hotel, Minneapolis, Minn. Deadline for submission of abstracts, Aug. 1, 1958. Secretary, Council on Scientific Assembly, Dr. Thomas G. Hull, 535 North Dearborn St., Chicago 10, Ill.

THE INTERNATIONAL CARDIOVASCULAR SOCIETY. *North American Chapter,* June 21, 1958, Sir Francis Drake Hotel, San Francisco, Calif. Secretary, Dr. Henry Haimovici, 105 East 90th Street, New York 28, N. Y.

INTERNATIONAL COLLEGE OF SURGEONS. *Alabama Surgical Division Meeting,* Medical College of Alabama, Birmingham, Oct. 30-31, 1958. Regent of Alabama, Dr. Paul Wolfe Shannon, 1927 First Ave. North, Birmingham 3, Ala. *Eastern Regional Meeting,* Equinox House, Manchester, Vermont, July 1-5, 1958. General chairman, Dr. M. Leopold Brodny, 636 Beacon St., Boston, Mass. *Mid-Atlantic Regional Meeting,* Homestead Spa, Hot Springs, Va., Nov. 17-18, 1958. Regent of Virginia, Dr. Elbyrne G. Gill, 711 Jefferson St. South, Roanoke 13, Va. *Fifth Annual Congress of the Japanese Section,* Tokyo, Japan, Oct. 17, 1958. For information write to the Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

INTERNATIONAL UNION AGAINST CANCER. *Seventh International Cancer Congress,* July 6-12, 1958, London, England. Secretary General, Harold Dorn, National Institute of Health, Bethesda 14, Md.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 3 and 4, 1958, Mount Washington Hotel, Burton Woods, N. H. Deadline for submission of papers, June 1, 1958. Secretary, Dr. Richard Warren, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 12-14, 1959, Denver, Colo. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.

THE SOCIETY FOR VASCULAR SURGERY. *Annual Meeting,* June 22, 1958, Sir Francis Drake Hotel, San Francisco, Calif. Secretary, Dr. Henry Swan, 4200 E. 9th Ave., Denver 20, Colo. All members of medical profession invited to attend Scientific Sessions of meeting.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 9-11, 1958, Boca Raton Hotel and Club, Boca Raton, Fla. Attendance by invitation of membership only. Secretary, Dr. George G. Finney, 2947 St. Paul St., Baltimore 18, Md.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.

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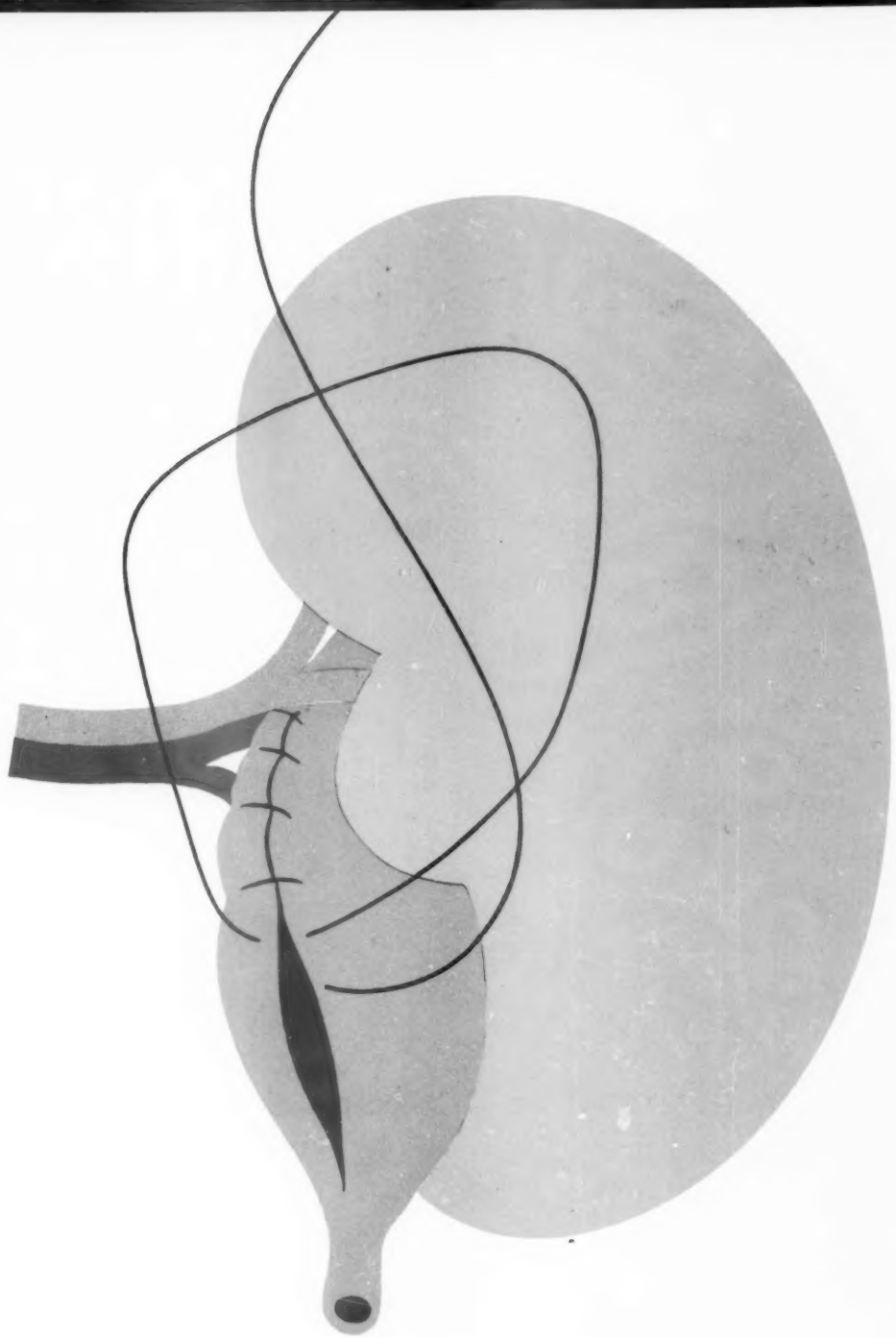

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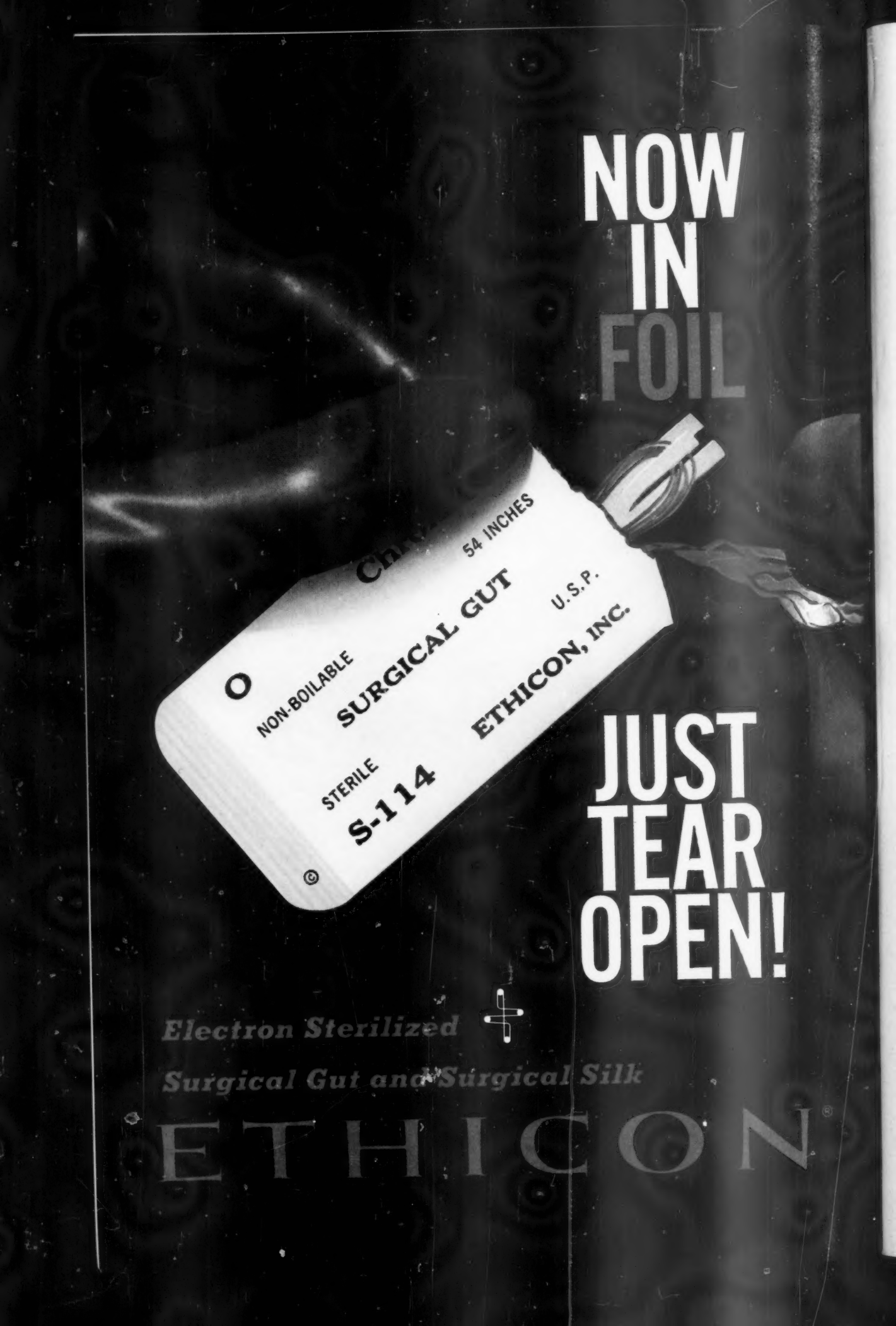
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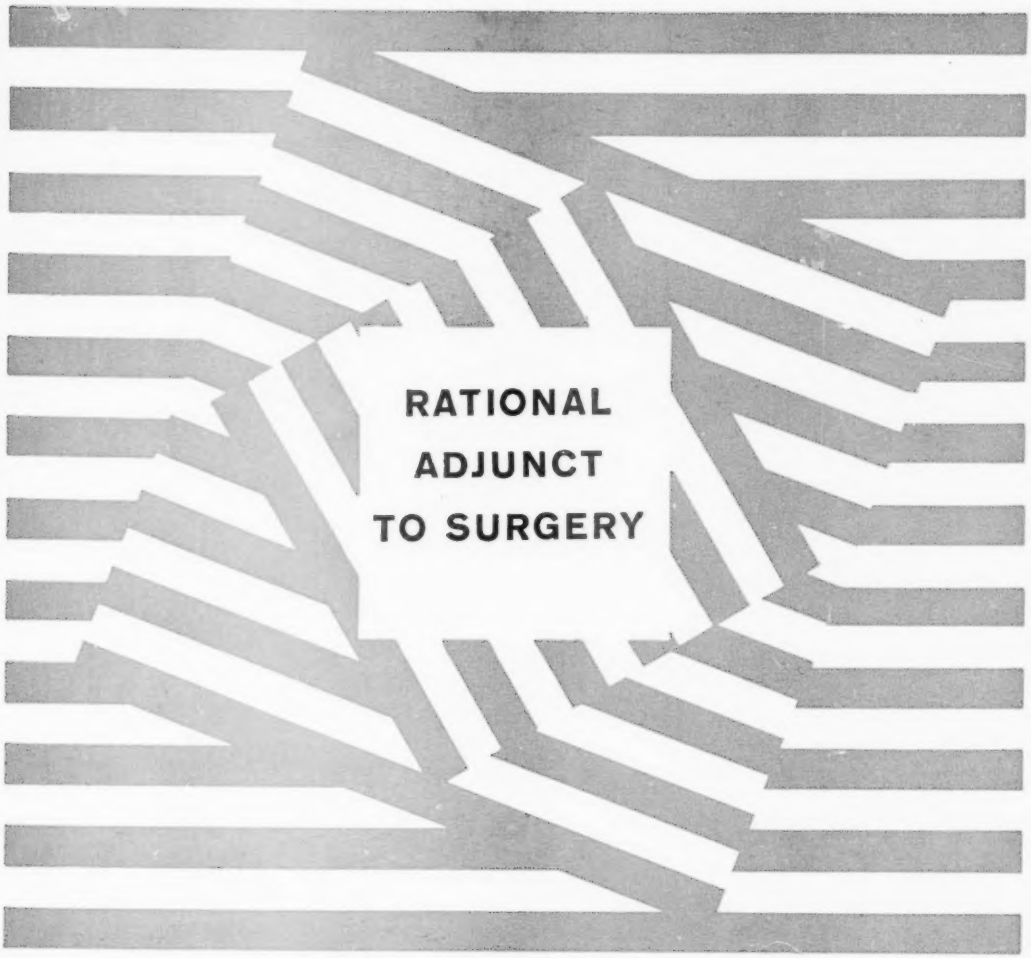

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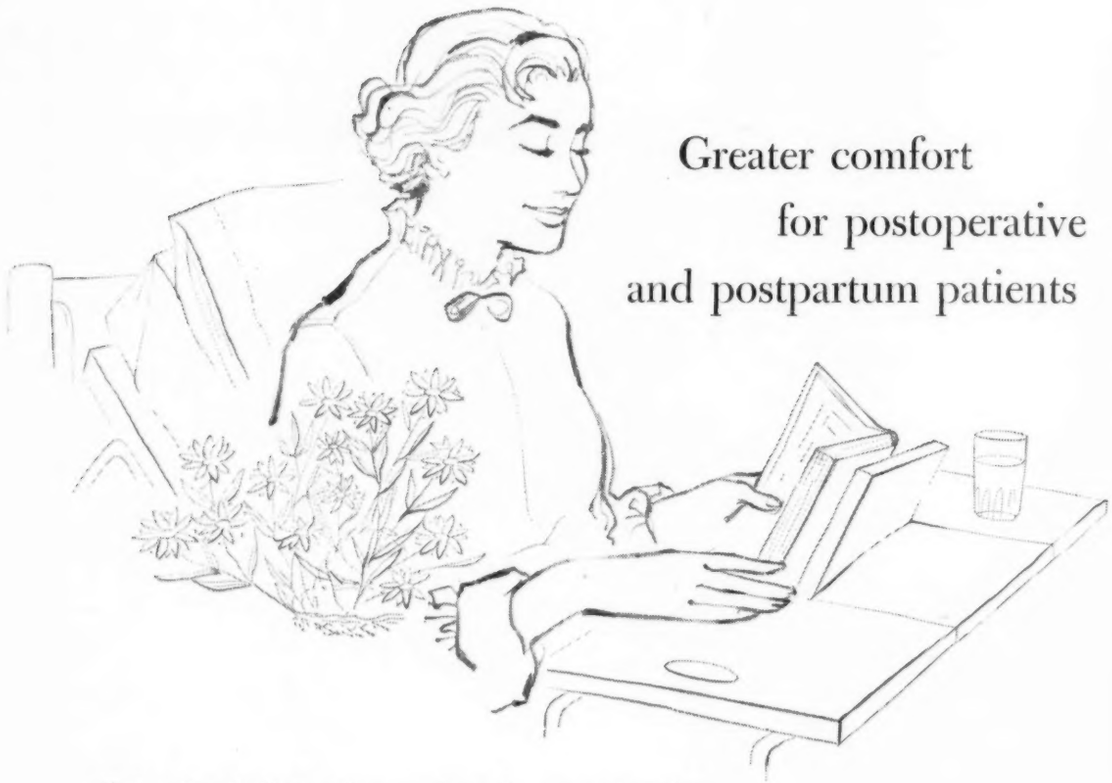

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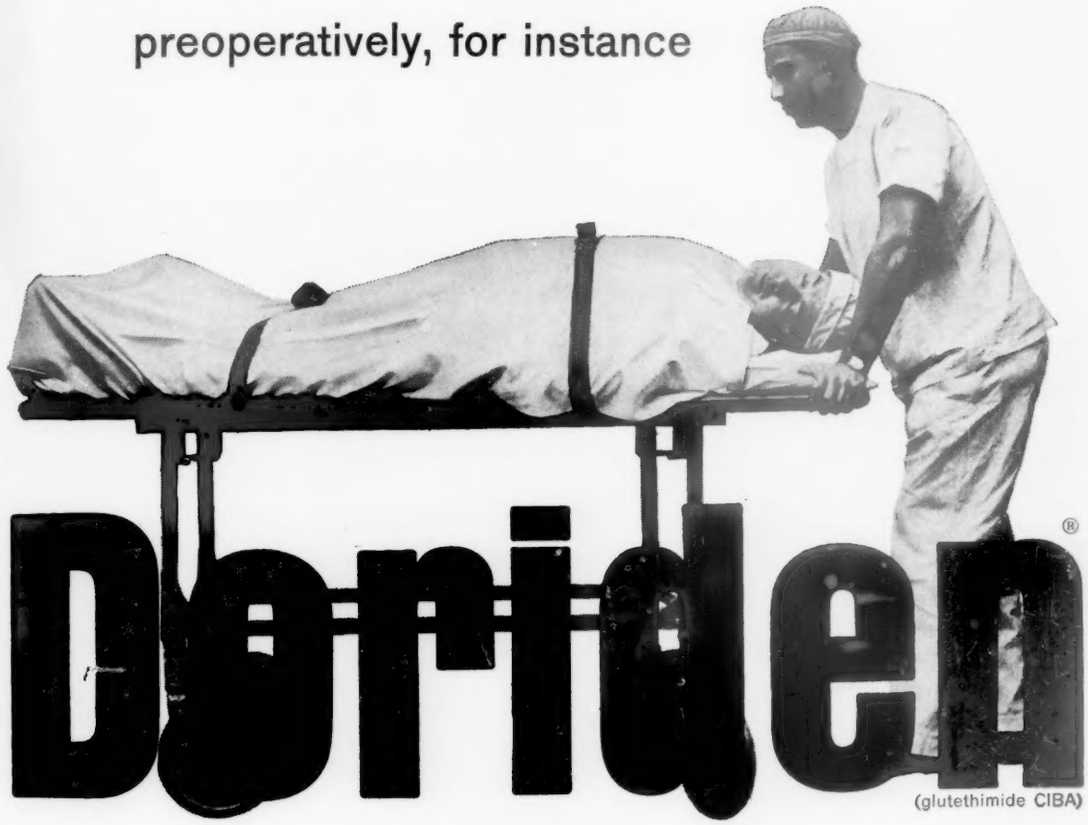

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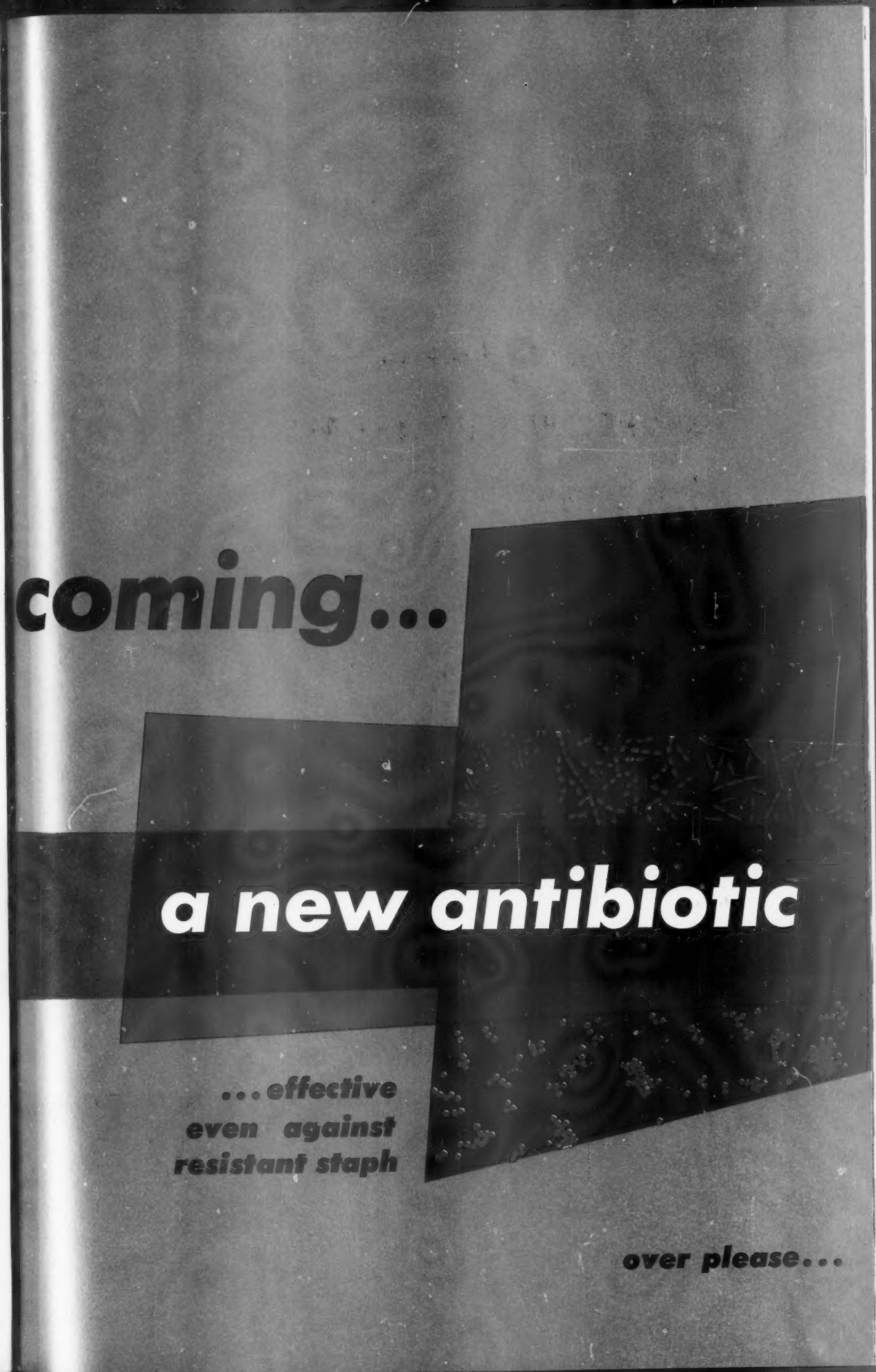
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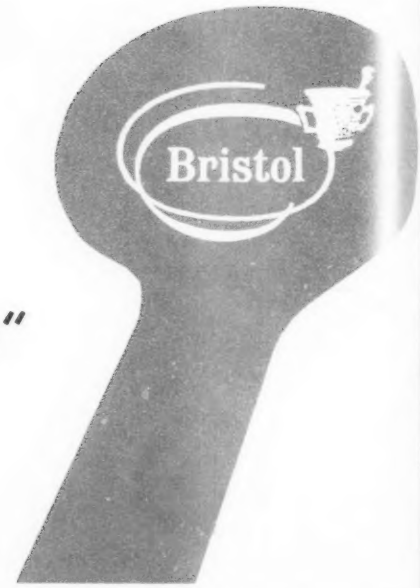

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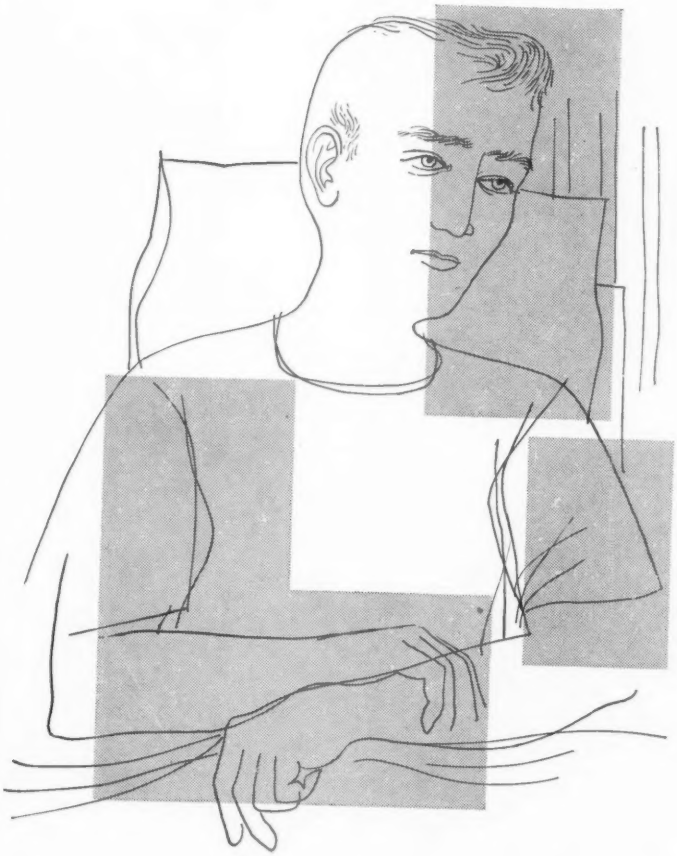

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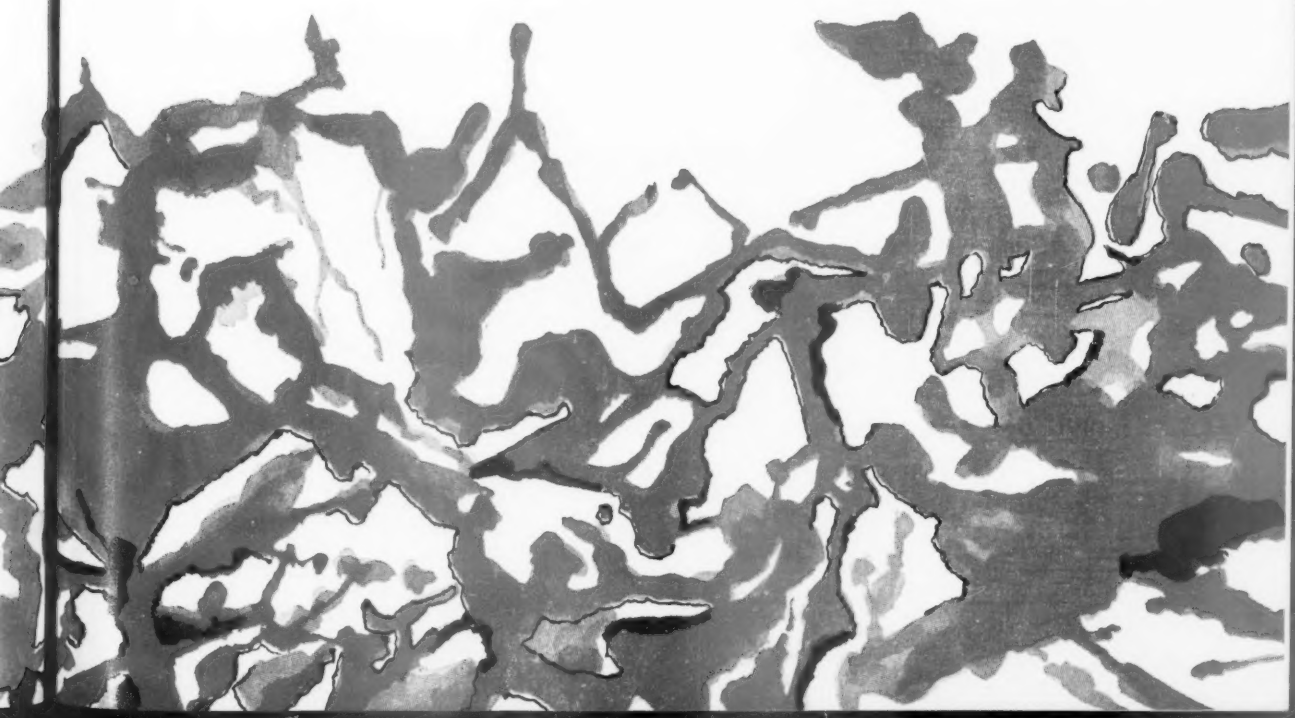
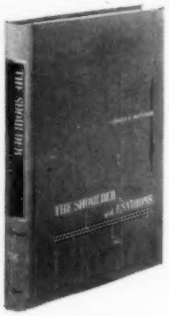


Stimulating Guidebook on Successful Diagnosis and Management of Problems of the Shoulder



THE SHOULDER AND ENVIRONS

By JAMES BATEMAN, M.D., F.R.C.S.(C)

Diplomate, American Board of Orthopaedic Surgery; Fellow, American Academy of Orthopaedic Surgeons; Orthopaedic Consultant, Sunnybrook Hospital, Toronto; Consultant, Workmen's Compensation Board of Ontario. 1955, 565 pages, 6¾" x 9¾", 376 illustrations. Price, $12.50.

• GIVES THE ANSWERS TO ALL OF YOUR SHOULDER PROBLEMS

Here is a book that gives a sound, systematic approach to all problems concerning the shoulder and environs. It simplifies diagnosis and treatment by correlating it with the practical complaint of the patient. Properly used, this book can help you give your patients better orthopedic care and can help you outline an effective program of treatment.

• PIN-POINTS DIAGNOSIS—THEN GIVES TREATMENT

In order to classify shoulder diseases and to pin-point diagnosis, symptoms are considered under three main headings: shoulder and neck pain; predominate shoulder pain; and shoulder plus radiating pain. By grouping separate disorders of the region in this manner, the individual lesion can be segregated and discussed in detail and successful therapeutic measure prescribed.

• DISCUSSES TREATMENT COMPREHENSIVELY

You can turn with confidence to this book for sound advice on treatment of all disorders. The chapter on "Differential Diagnosis" includes tabular summaries of the common entities of each group for quick reference. Following the classification of the symptoms, the individual lesions are discussed in detail including the pathology, clinical course and treatment. Copiously-illustrated with 376 photographs and drawings, this book contains detailed illustrations of all the standard and new operative procedures.

• DESCRIBES METHODS OF FRACTURE TREATMENT AND NEUROLOGICAL DISORDERS

Dr. Bateman authoritatively evaluates the various methods of fracture treatment and indicates his preference. You'll welcome the detailed consideration of nerve injuries and neurological disorders, not only because of their increasing incidence, but because of their serious effects on regions apart from the shoulder.

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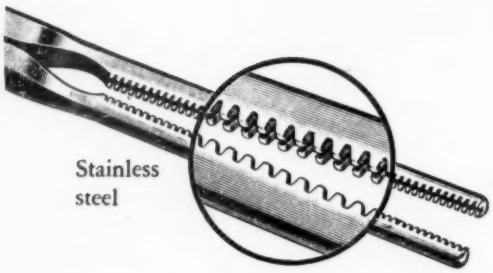

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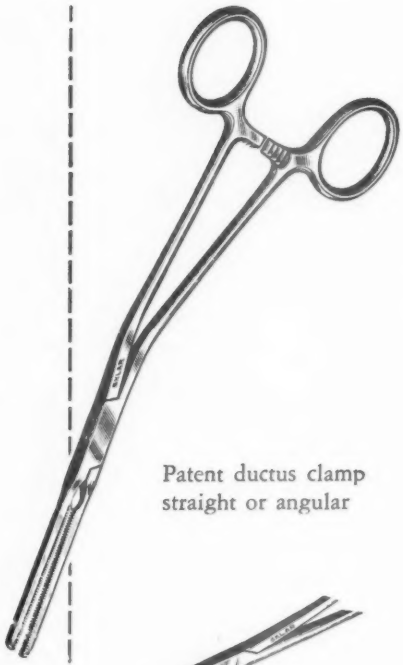
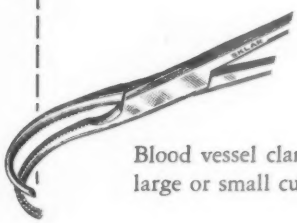


Patent ductus clamp
straight or angular

Satinsky
vena cava clamp

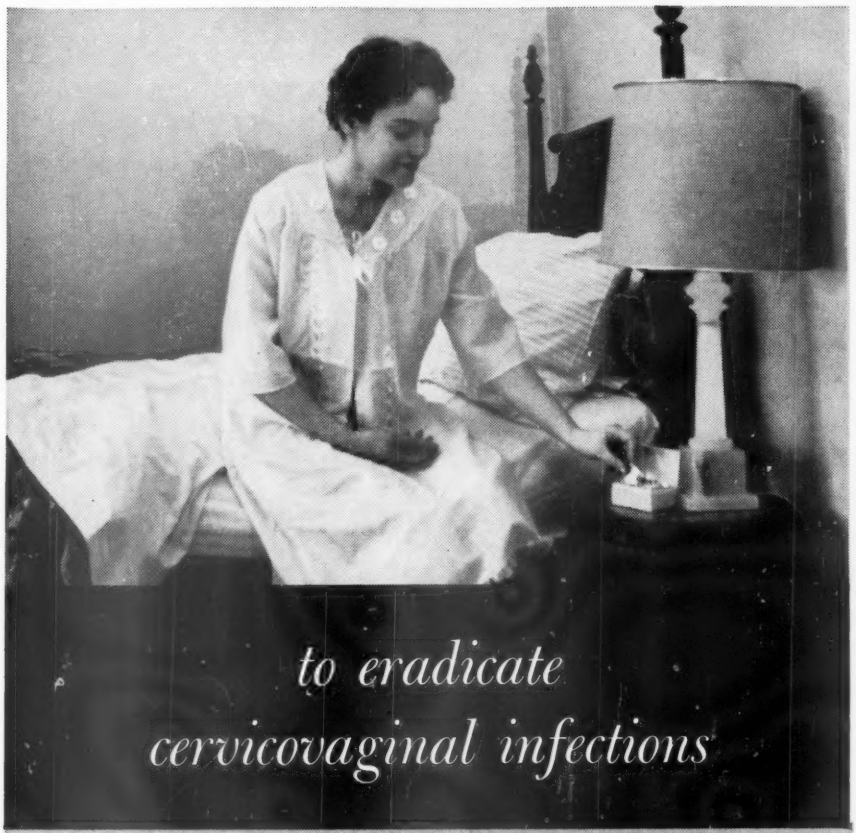


Blood vessel clamp
large or small curve

Coarctation clamp
straight or angular

Bronchus clamp, angular

Bulldog clamp
2", 2½" 3", 3½"



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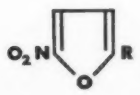

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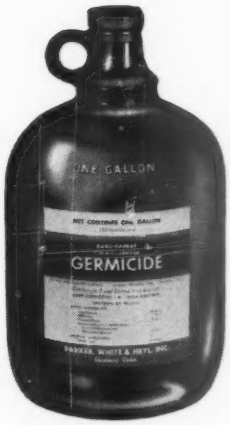

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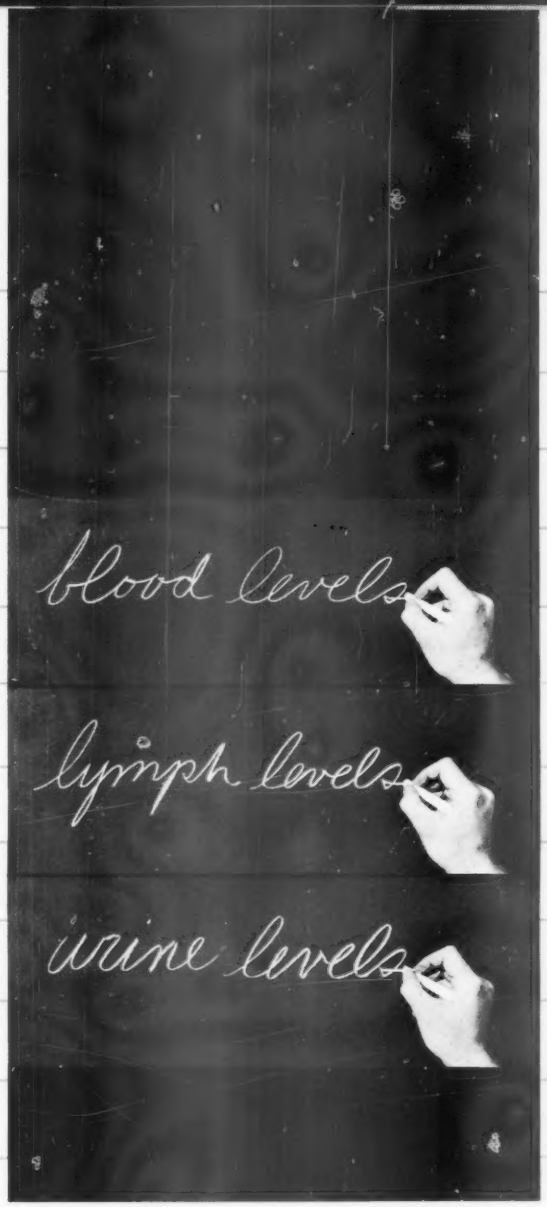

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2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

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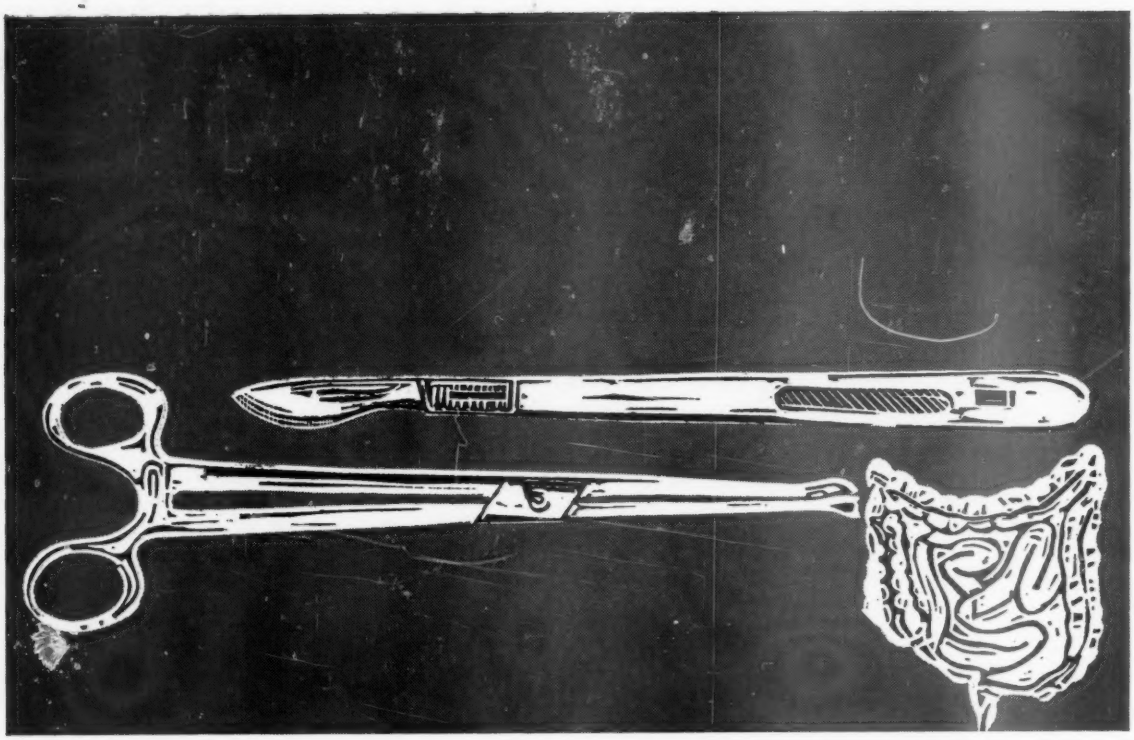

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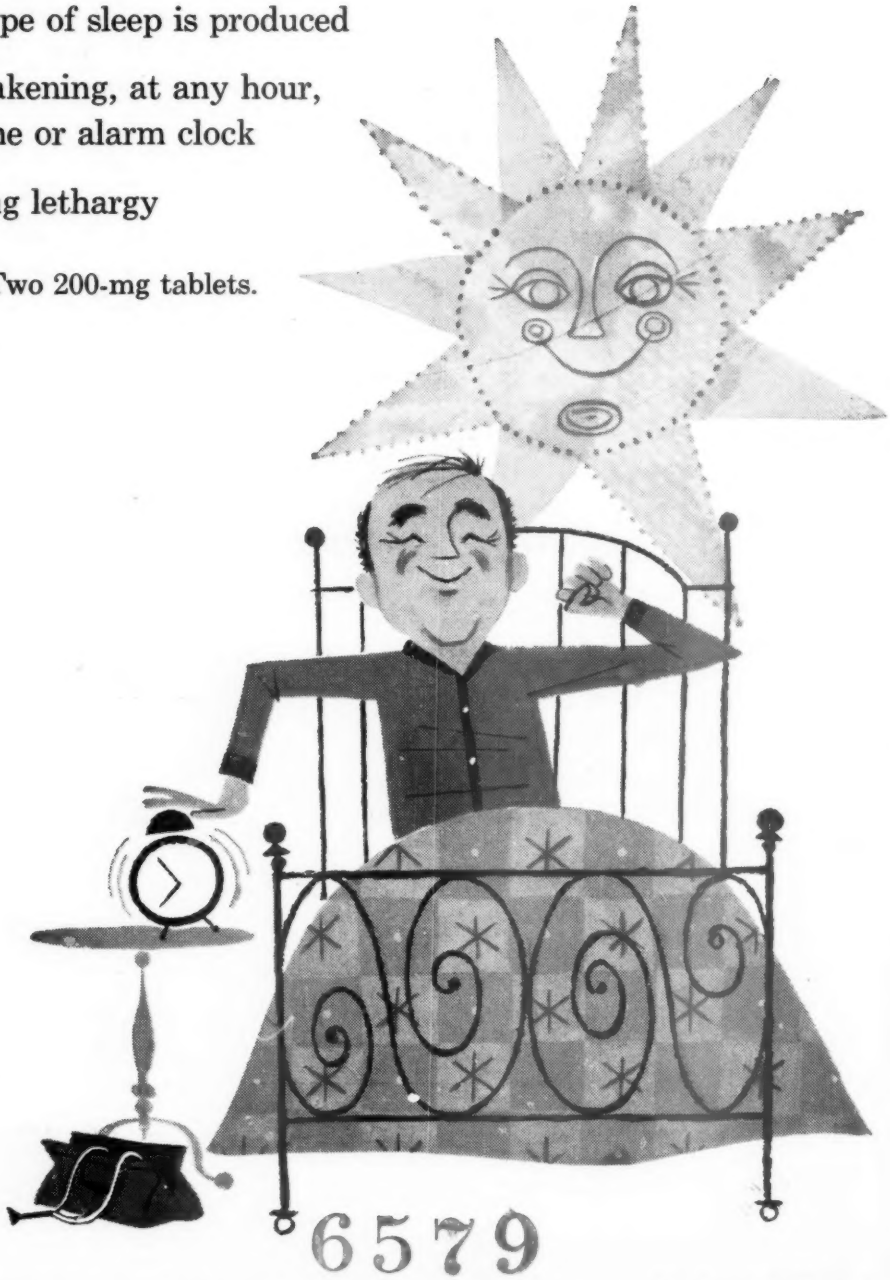

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